

Volume 1



ADVANCES IN **COSMETIC SURGERY**

EDITORS

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Jeffrey S. Dover
Heather J. Furnas
Marissa M.J. Tenenbaum
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2018

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Director, Continuity Publishing: Taylor Ball
Editor: Jessica McCool
Developmental Editor: Donald Mumford

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Printed in the United States of America.

Editorial Office:
Elsevier, Inc.
1600 John F. Kennedy Blvd,
Suite 1800
Philadelphia, PA 19103-2899

International Standard Serial Number: 2542-4793
International Standard Book Number: 13: 978-0-323-63963-7

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Now more than ever before, individuals are looking to improve their cosmetic appearance. Social media and Reality TV stars have largely changed the way people look at themselves, and the desire to enhance physical appearance is rapidly growing. Advancements in cosmetic surgery have made a wide variety of options available to those wishing to make these enhancements.

Advances in Cosmetic Surgery highlights the year's latest advancements and breakthroughs in the field of cosmetic surgery from a multispecialty approach. Our aim in compiling these topics has been to showcase the latest trends that would be of most interest to plastic surgeons, facial plastic surgeons, cosmetic dermatologists, and oculoplastic surgeons. These specialties are all represented within our editorial board, and we are confident that we've assembled the leading experts to discuss these cutting-edge topics.

Fillers, body contouring, facial rejuvenation, lasers, fat reduction, and scar treatment are just some of the topics covered in this issue. High-quality images and videos accompany many of these articles as well, so that readers can gain a deep understanding of these advancements and apply their learning to their own daily practice. Whether you are planning to perform the procedures discussed here or are learning about them for

the first time, we think you will find value in what this exciting new series has to offer.

The editors would like to thank the authors for their stellar contributions, and Alan Matarasso, MD, from Hofstra University/Northwell School of Medicine, for his assistance in developing the concept of this series and the topics for this volume.

It is our hope that this publication will serve as a convenient way for cosmetic surgeons to stand at the forefront of this exciting specialty, as we all seek to keep pace with the ever-evolving vision of cosmetic beauty.

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Preface

A Look at What's New and What's Coming in Cosmetic Surgery



Heather J. Furnas, MD, FACS
Editor

As we look back through the decades, we see that cosmetic surgery has broadened its reach far beyond the knife. Technological advances have refined our surgical techniques and given us more options, while expanding the frontier of noninvasive and minimally invasive procedures. As we look to ways of looking younger, thinner, tighter, less sun-damaged, and more fit, it is important to identify the new technologies that truly work. The following articles present experts' experience with an array of new advances in cosmetic surgery, including hormones to combat aging, heat for tightening, cold for fat reduction, new uses for fillers and neuromodulators, fat transfer, and the use of platelet-rich plasma. While there will always be a place for surgery, patients will continue to seek nonsurgical treatments to look their best.

Just as important as offering the latest and greatest cosmetic modalities is knowing the limits of each and their potential risks and complications. Is liposuction, deoxycholic acid, or cryolipolysis the best way to address submental fullness? Is filler or fat transfer the best way to treat periorbital aging? The options are

many, and the aim of this volume is to help you know what to look for in assessing a patient.

Some treatments have been used for many years, such as fillers, but as their usage has increased, so has the number of complications. Learning how to avoid and treat a vascular occlusion is as important as knowing how to get a good result. Platelet-rich plasma, on the other hand, is gaining popularity, and its usage and benefits are currently being defined.

While the field of cosmetic surgery can sometimes seem like the Wild West, the aim of this volume is to present an array of surgical and nonsurgical treatments so that you can offer the very best options to your patients.

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Nonsurgical Treatment of Submental Fullness



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KEYWORDS

• Submental fullness • Preplatysmal fat • Kybella • Deoxycholic acid • Coolsculpting • CoolMini • Cryolipolysis

KEY POINTS

- Submental fullness is a prevalent concern among cosmetic patients, historically treated with liposuction or surgical intervention.
- Newer methods of submental fat reduction have been developed in recent years, offering noninvasive outpatient techniques that have the benefit of less downtime and associated risks.
- Kybella is a synthetic form of injectable deoxycholic acid developed and approved by the Food and Drug Administration for the treatment of moderate to severe submental fat.
- Cryolipolysis is an alternative method of reducing submental fat via controlled cooling. The CoolMini applicator for the Coolsculpting device is designed specifically for the submental region.



Video content accompanies this article at www.advancesincosmeticsurgery.com.

INTRODUCTION: NATURE OF THE PROBLEM AND NONINVASIVE APPROACHES

Submental fullness is a common presenting complaint among cosmetic patients that often presents a difficult therapeutic challenge. A youthful and aesthetically pleasing neck includes features such as a well-defined mandibular border, a cervicomental angle of 105 to 120°, and visible landmarks including the anterior border of the sternocleidomastoid, thyroid cartilage, and subhyoid depression [1]. Neck fullness with aging can be due to a variety of factors, including skin laxity, pre- and subplatysmal subcutaneous fat accumulation, or a combination thereof. Younger patients also may have a full-appearing neck due to anatomic variation,

including retrognathia or a low/anterior hyoid position. This article focuses specifically on treatment of submental fullness due to excess adipose tissue in the preplatysmal compartment, which is amenable to noninvasive approaches. Skin laxity may be addressed with surgical rhytidectomy and neck-lifting, or noninvasive tightening devices discussed elsewhere. Retrognathia may be addressed with chin augmentation using implants or deep filler placement. Fat accumulation beneath the platysma (subplatysmal) is more appropriately addressed with surgical lipectomy with or without submentoplasty [2,3].

Submental fat accumulation obscures the mandibular line and contributes to an overweight and aged appearance. This can be a stubborn area of fat

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deposition, often unresponsive to lifestyle modifications such as diet and exercise. Genetic predisposition to accumulation of submental adipose tissue, as well as normal aging, can create discordance between submental fullness and overall body mass index. Reduction can significantly improve patient satisfaction in appearance [2].

Historically, invasive procedures, including liposuction, rhytidectomy, and submentoplasty, were the mainstay of treatment to reduce fullness in the submental region; however, these surgical procedures carry surgically related risks and often require prolonged recovery times [2–6]. In more recent years, multiple less-invasive nonsurgical modalities have been developed to address this concern. Several devices are available to treat neck redundancy and stimulate skin tightening, using ultrasound and radiofrequency modalities; however, this does not address unwanted fullness due to lipohypertrophy.

More recently, methods of fat destruction have become available to target this concern with a less-invasive approach. The molecule ATX-1010 (Kybella [United States]; Allergan, Inc., Dublin, Ireland) is an injectable form of synthetic deoxycholic acid (DCA) approved by the Food and Drug Administration (FDA) in 2015 for the treatment of moderate to severe fullness of the submental fat compartment. The safety and efficacy of ATX-1010 has been studied in a total of 18 Phase I to III clinical trials, including 4 randomized, double-blind, placebo-controlled Phase III clinical trials in Europe, the United States, and Canada [7–17]. Statistically significant reduction in submental fullness was demonstrated via patient-reported outcome assessments and caliper measurements in all 4 Phase III trials, and additionally via MRI in the REFINE 1 and 2 trials [12–14].

Endogenous DCA is a bile acid important in solubilization, breakdown, and absorption of dietary fats in

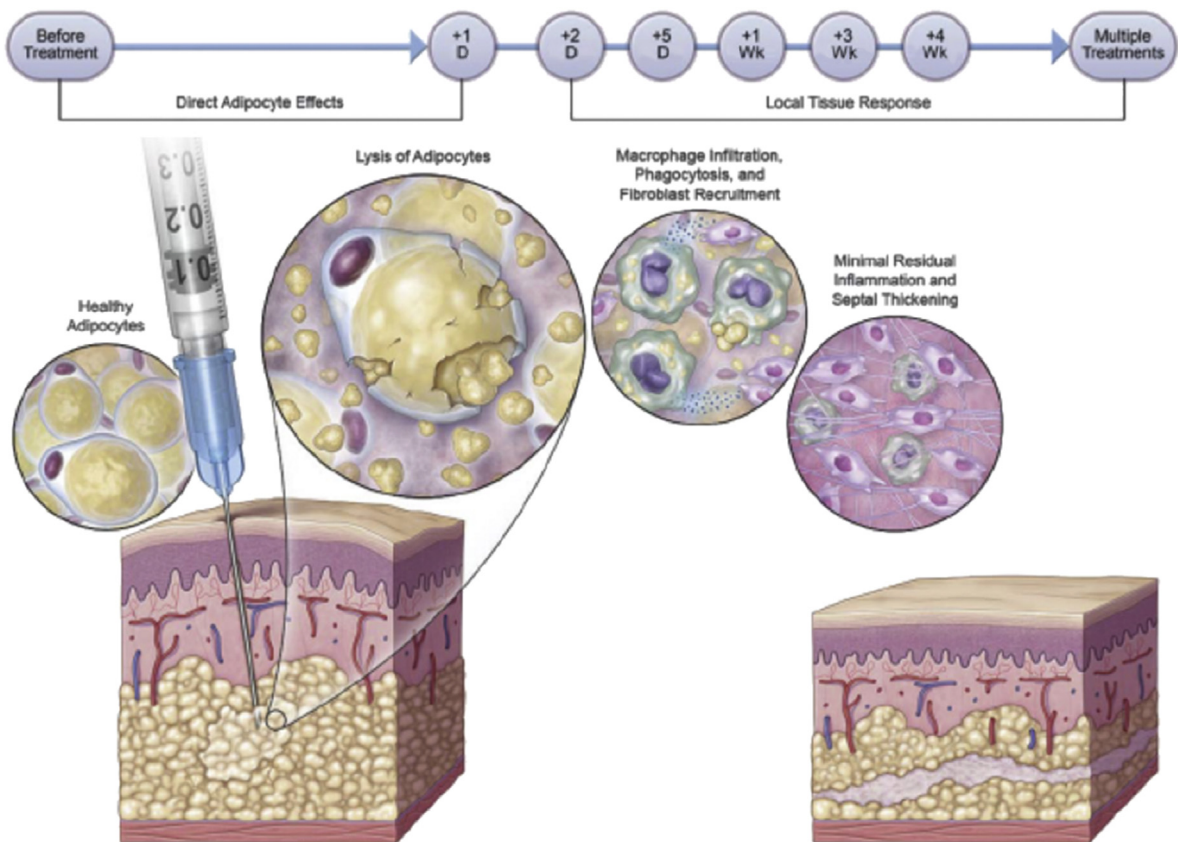


FIG. 1 Mechanism of action of DCA. (From Dayan SH, Humphrey S, Jones, DH, et al. Overview of ATX-101 (deoxycholic acid injection): a nonsurgical approach for reduction of submental fat. *Dermatol Surg* 2016;42:S265; with permission.)

the gastrointestinal tract. When injected into subcutaneous fat, synthetic DCA causes adipocytolysis by physically disrupting the adipocyte cell membrane. This in turn results in macrophage and fibroblast recruitment with clearance of cellular debris and stimulation of fibrosis [1] (Fig. 1). Given the definitive destruction of adipocytes following treatment, the results following DCA injection are likely to be sustained long-term.

An alternative noninvasive method of submental fat reduction uses cryolipolysis, in which controlled cooling of the tissue induces a lobular panniculitis (CoolSculpting; ZELTIQ, Pleasanton, CA). This triggers an inflammatory response and apoptosis-mediated loss of adipocytes [18]. Cold temperatures are used to induce selective adipocyte damage with minimal collateral damage to surrounding tissues, including the epidermis. This modality was originally FDA approved for fat reduction on the trunk and thighs in 2010. A smaller applicator was later approved in 2015 for treatment of submental fat (CoolMini; ZELTIQ, Pleasanton, CA) and proven to be efficacious in reducing submental fullness [19].

DEOXYCHOLIC ACID

Surgical Technique

Preoperative planning

Careful patient selection is critical when considering treatment with DCA. Patients with moderate or greater submental fullness should be deemed appropriate candidates when fullness is demonstrated to be due to preplatysmal fat accumulation. This can be assessed by having the patient flex the platysmal muscle while palpating the preplatysmal fat pad in the submental region. Preplatysmal fat can be grasped and palpated above the platysma with simultaneous platysmal engagement [4].

DCA injections should be avoided in patients with submental concavity largely due to marked submental laxity, rather than fat deposition. Patients with significant skin laxity may be more amenable to nonsurgical tightening devices or surgical intervention. Patients with a history of submental/anterior cervical surgery, or a history of facial nerve paralysis or dysphagia are not optimal candidates for DCA injection. Clinicians also should avoid injecting into actively inflamed or indurated tissue.

Another important feature to note before treatment is the presence of prominent platysmal bands, which may be accentuated following reduction of preplatysmal fat. This should be discussed with the patient in detail. If platysmal bands are accentuated posttreatment, this can be addressed with neuromodulators or surgical intervention (platysmaplasty) [4].

When examining a patient for pretreatment assessment, the submental region should be carefully inspected to rule out other causes of submental fullness, such as thyromegaly, salivary gland enlargement, or lymphadenopathy. The patient should be examined in the upright and supine positions to fully assess cervical fullness. Before treatment, clinicians also should carefully assess swallowing to rule out dysphagia, as well as smile symmetry to assess marginal mandibular nerve function [20].

Reasonable expectations should be discussed before treatment. A range of 1 to 6 treatments may be required to achieve satisfactory results. The number of treatment sessions should be tailored to the individual and severity of fullness before onset of treatment. Severity of submental fullness can be assessed by referencing the validated Clinician-Reported Submental Fat Rating Scale used during Phase III clinical trials (Fig. 2). Determining severity before treatment can help with estimating the number of treatments that will be required. Most patients will see a noticeable difference within 2 to 4 treatments [1]. In the authors' experience, most patients with moderate severity require 2 to 3 treatments.

Treatment sessions should be spaced 1 month or more apart, with 6 weeks being optimal in the authors' experience. Common adverse effects, discussed further in future sections, should be fully counseled with the patient. It is also worth noting that Kybella treatments can cost \$1000 to \$2000 per treatment, and if multiple treatments are required it may be cost-prohibitive for some patients.

Complete knowledge of relevant cervical and submental anatomy is essential before patient treatment. Importantly, the marginal mandibular branch of the facial nerve is susceptible to injury following DCA injection. The marginal mandibular nerve (MMN) innervates numerous muscles that depress the lower lip, including the depressor anguli oris, depressor labii inferioris, orbicularis oris, and mentalis. The MMN exits from beneath the masseter muscle at the antegonial notch, curving slightly beneath the mandibular border before coursing upward to innervate lower facial muscles (Fig. 3). The nerve passes over the mandible with the facial artery and vein at the antegonial notch, which can be palpated at the anterior border of the clenched masseter muscle along the mid-mandible. It is worth noting that in middle-age and beyond, the MMN drops beneath the mandibular border, making it more susceptible to injury during procedures in the

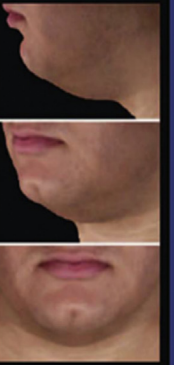
Scale	0	1	2	3	4
Submental Convexity	Absent	Mild	Moderate	Severe	Extreme
Description	No localized submental fat evident	Minimal localized submental fat	Prominent localized submental fat	Marked localized submental fat	Extreme submental convexity
Representative Photographs					

FIG. 2 The validated Clinician-Reported Submental Fat Rating Scale. (From McDiarmid J, Ruiz JB, Lee D, et al. Results from a pooled analysis of two European, randomized, placebo-controlled, phase 3 studies of ATX-101 for the pharmacologic reduction of excess submental fat. *Aesthetic Plast Surg* 2014;38:851; with permission.)

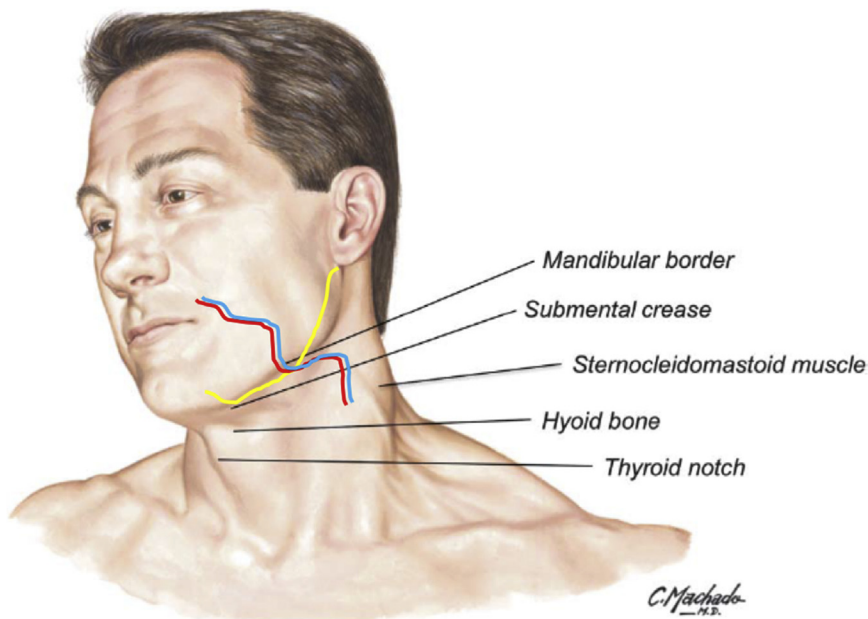


FIG. 3 Anatomy of the anterior neck with important anatomic landmarks. MMN is shown in yellow. Facial artery and vein are shown in red and blue, respectively. Copyright © 2018. Netter illustration used with permission of Elsevier, Inc. All rights reserved. www.netterimages.com.

upper neck. Direct injection of active drug should be avoided within the path of this nerve. Damage will result in temporary inability to depress the lower lip unilateral to the side of damage and smile asymmetry [21].

Preparation and patient positioning

1. The patient should be positioned comfortably in a semi-upright position, with the head reclined slightly and resting against a headrest.
2. Clean the skin thoroughly with antiseptic solution.
3. With surgical pen, mark anatomic boundaries of the preplatysmal fat (Fig. 4), which include the following:
 - Inferior mandibular border and submental crease inferior to this, which comprises the superior boundary
 - By marking a line 1.0 to 1.5 cm below the mandibular border, this outlines a zone to avoid treatment where the MMN may course beneath the mandible as it crosses at the antegonial notch
 - Hyoid bone inferiorly
 - Line drawn inferiorly as a continuation from the labiomandibular fold, which creates the lateral boundaries of the preplatysmal fat

The optimal concentration per treatment area in clinical trials was found to be 2 mg/cm², which was more effective than 1 mg/cm² [2]. A higher concentration of 4 mg/cm² was found to have greater risk of adverse events

without benefit of greater efficacy. Kybella is provided in 10 mg/mL concentration, which correlates to 2 mg/cm² when injected in 0.2-mL aliquots at 1-cm intervals. Plan for injections spaced 1 cm apart by using the included temporary tattoo grid, superimposed onto the treatment area (see Fig. 4). The volume (in milliliters) of DCA needed can be calculated by counting the number of tattoo grid injection points with the boundaries drawn, divided by 5 (as 0.2 mL is delivered per injection). Suggested delivery is via 1-mL syringes with a half-inch 30-gauge needle [20]. Measures to reduce pain are outlined in the “Rehabilitation and recovery” section.

Procedural approach

1. Prepare the patient as described previously with anatomic markings and the provided temporary tattoo grid for injection spacing (Fig. 5).
2. Begin at most lateral point on the most inferior row. Pinch the preplatysmal fat between 2 fingers, insert the needle perpendicular to skin into mid-subcutaneous fat (Fig. 6). Avoid pinching skin or injecting too superficially, which can lead to skin necrosis. Inject the first 0.2-mL aliquot into the first injection site.
3. Continue injecting 0.2-mL aliquots in each injection point, moving horizontally along the bottom row.
4. Once the bottom row is completed, move upward row by row until each injection point has been completed. Injections should end at a lateral edge of the most superior row.

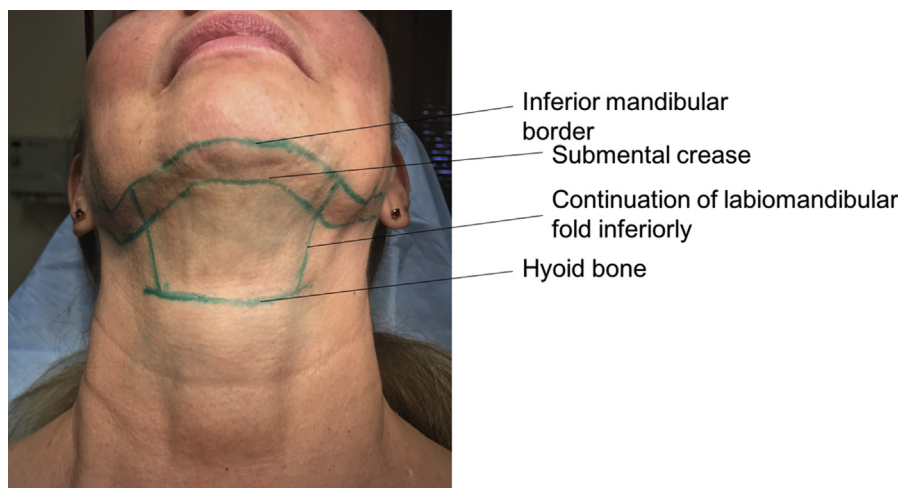


FIG. 4 Anatomic boundaries of the preplatysmal fat, marked before injection with DCA. Borders include the submental crease superiorly, caudal continuation of the labiomandibular folds laterally, and the hyoid bone inferiorly. Treatment should not be delivered in the gap between the inferior mandibular border and the submental crease, as risk of injury to the MMN is greater in this region.

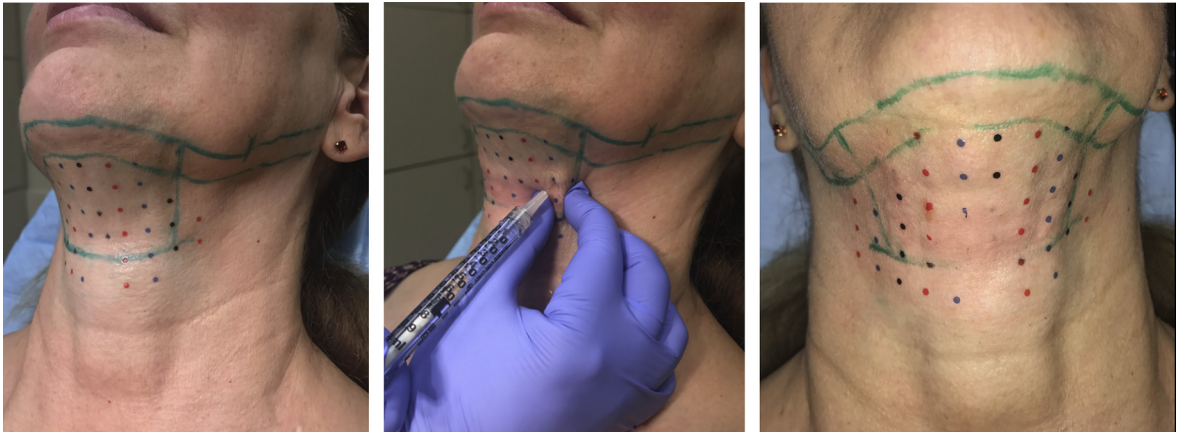


FIG. 5 Temporary tattoo grid markings within the treatment area for DCA injection shown before, during, and immediately after injection.

5. The maximum recommended amount of injection volume is 10 mL per treatment session [1,22].

6. Repeat treatment sessions at a minimum of 28-day intervals. Inflammation has been histopathologically demonstrated to have resolved by this time [1].

7. See Video 1.

Rehabilitation and recovery

Common treatment reactions following injection of DCA include pain, swelling, bruising, erythema, numbness, induration, and, less commonly, pruritus, paresthesia, and subcutaneous nodule formation. Among the US-based REFINE trials, the most common reported symptoms included pain (70%), bruising (72%), and edema/swelling (87%) [23]. Pruritus was reported to occur less commonly in 8.6% to 42.0% of patients, and paresthesia in 12.8% to 38.0% [7,8]. Patients should be advised to anticipate mild edema and induration for up to 4 weeks. Patients should be advised to call if they notice asymmetry in smile or increased difficulty in swallowing following treatment.

Pain can range from mild to severe in intensity. Measures to reduce pain include cold compresses, topical and injectable anesthetic, oral analgesics, oral antihistamines, and application of a chin strap posttreatment. In 1 study of 83 patients, the use of both topical and injectable anesthetics decreased peak pain by 17% when compared with cold compresses alone. The addition of oral ibuprofen and oral loratadine before treatment, in addition to topical and injectable anesthetic, further decreased peak pain by 40% [20]. Measures to reduce pain are outlined in Table 1.

Bruising is common and occurred in 53.7% to 72.9% of patients treated with ATX-101 among the Phase III clinical trials [24]. Measures to reduce

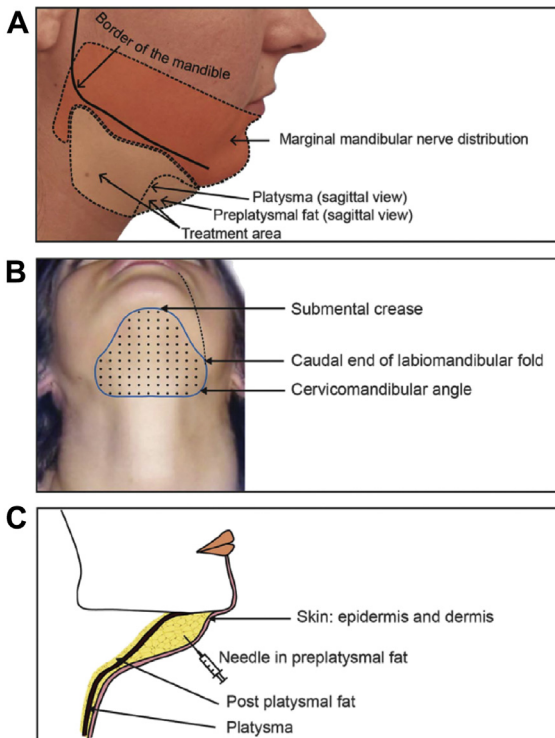


FIG. 6 Landmarks (A), injection points (B), and treatment depth (C) of submental fat with DCA. (Courtesy of Sachin M. Shridharani, MD, LUXURGERY, New York, NY; with permission.)

TABLE 1
Measures to Reduce Posttreatment Pain
Following Deoxycholic Acid Injection

Treatment	Comments
Cold compresses	Applied 10–15 min pretreatment and posttreatment
Topical anesthetic	4% lidocaine cream applied under occlusion 45 min prior
Injectable anesthetic	1% lidocaine with epinephrine (1:100,000) within the area of treatment 15–30 min prior - Direct injection into the subcutaneous fat or infiltration with cannula
Oral antihistamine	Loratadine 10 mg orally once daily for 7 d pretreatment and posttreatment
Oral analgesic	- Ibuprofen 600 mg, 1 h prior, continued 3 times daily for 3 d posttreatment - Acetaminophen 650 mg orally 1 h before treatment
Chin strap	Applied 15 min posttreatment and worn for at least 24 h

Adapted from Dover JS, Kenkel JM, Carruthers A, et al. Management of patient experience with ATX-101 (deoxycholic acid injection) for reduction of submental fat. *Dermatol Surg* 2016;42:S292; and Fagien S, McChesney P, Subramanian, et al. Prevention and management of injection-related adverse effects in facial aesthetics: considerations for ATX-101 (deoxycholic acid injection) treatment. *Dermatol Surg* 2016;42:S302; with permission.

bruising are similar to those to reduce hemorrhage with other surgical procedures and include discontinuation of oral agents that increase bleeding risk 7 to 10 days

prior [23]. The authors do not recommend discontinuation of medically necessary blood thinners for patients who have had cardiovascular or clotting events. The vasoconstrictive effect of injected anesthetic with epinephrine may reduce the risk of significant purpura formation. Bothersome bruising can be managed in the posttreatment period with pulsed-dye laser therapy.

Clinical results in the literature

Phase III clinical trials reported a clinically significant difference in submental fullness reduction, supporting the efficacy of DCA. Patients with moderate to severe fullness were included based on a 5-point scale, as presented in the “Preoperative planning” section (see Fig. 2). Overall, 52% of subjects achieved a 1 or greater grade improvement in submental fullness after the second treatment with DCA. After the fourth treatment, this number increased to 72% of subjects. These results were verified with caliper measurements and MRI [24,25]. MRI response rate was 46.3% and 40.2% reduction with the REFINE 1 and 2 phase III trials, respectively, both with a *P* value of less than .001. Submental fat thickness was reduced by a mean of 21.9 and 17.8 mm from baseline, in each study, both with a *P* value of less than 0.001. An overview of the Phase III clinical trials is presented in Table 2. Representative results are shown in Fig. 7.

Phase IIIb studies for ATX-101 are ongoing in which partial and complete responders at 12 weeks posttreatment are being followed to monitor for sustained response. Most patients have been shown to maintain partial (87.5%–95.4%) or complete response (87.4%–90.4%) at 1-year and 2-year follow-up intervals [25]. Ongoing 5-year follow-up studies of responders have yet to be reported. Considering the cytotoxic

TABLE 2
Overview of Phase III Clinical Trials for ATX-101

Study	Authors	Number of Subjects	Concentration of ATX-101, mg/cm ²	% With 1 or Greater Improvement on 5-Point Scale	<i>P</i>
European Phase III	Ascher et al [9], 2014	119	1	59.2	<.001
		121	2	65.3	<.001
European Phase III	Rzany et al [11]	121	1	58.2	<.001
		122	2	68.3	<.001
US/Canadian Phase III (REFINE-1)	Jones et al [8], 2016	256	2	70.0	<.001
US/Canadian Phase III (REFINE-2)	Humphrey et al [12], 2014	258	2	66.5	<.001

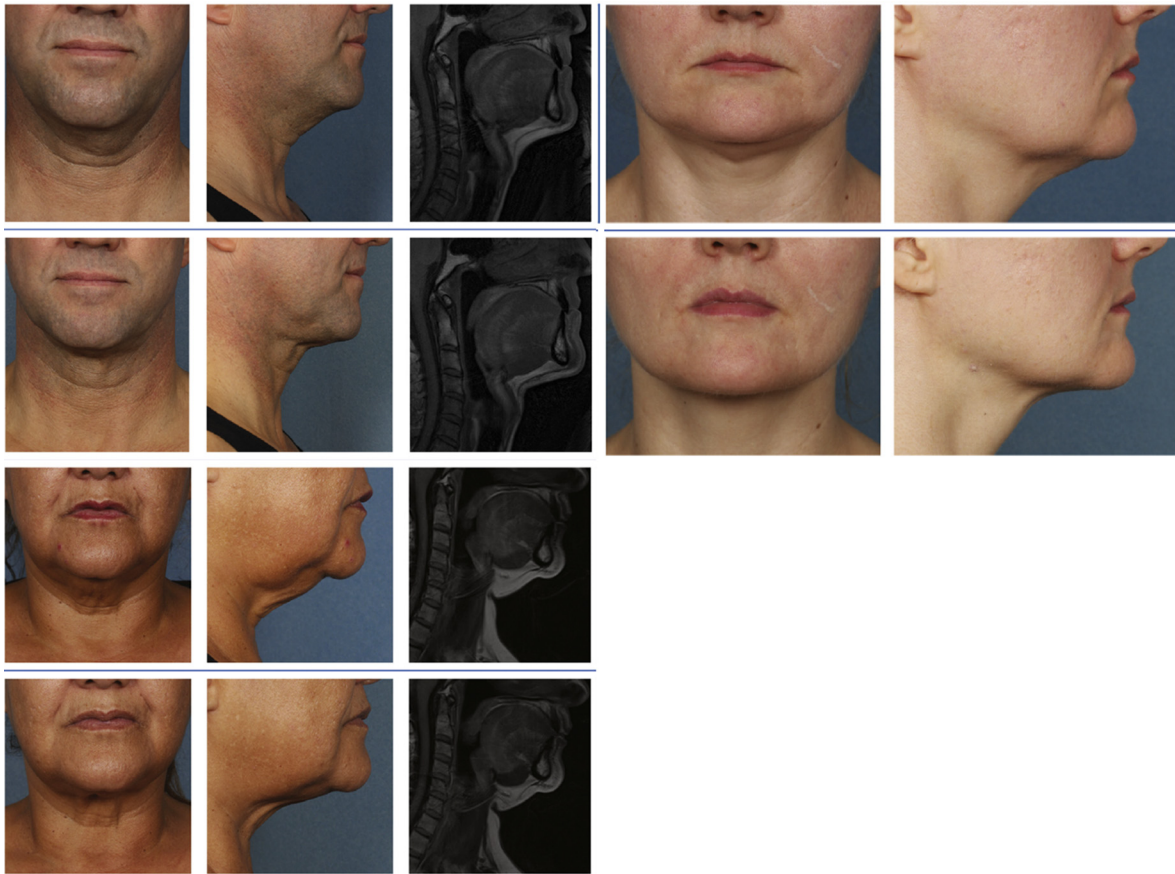


FIG. 7 Treatment results from Phase III randomized clinical trials. (*Adapted from* Humphrey S, Sykes J, Kantor J, et al. ATX-101 for reduction of submental fat: a phase III randomized controlled trial. *J Am Acad Dermatol* 2016;75(4):792–3; with permission.)

mechanism of DCA, resulting in adipocyte cell death, it is reasonable to propose that fat reduction following treatment will be sustained. However, long-term durability of clinical results has yet to be determined.

Potential Complications/Risks/Benefits/Limits

The most common side effect of DCA is immediate posttreatment pain, which can be moderate to severe in intensity. However, this is usually limited to a day or less in duration [20,23] and can be reduced by measures outlined in Table 1.

MMN paralysis is a known risk factor with DCA injection and occurred in 4.3% (11/258) of patients treated with ATX-101 among the REFINE Phase III randomized controlled trials [12,13]. All incidences were described as mild to moderate in severity. Recovery time varied widely, ranging from 7 to 60 days. One severe case of

MMN paralysis occurred and resolved at 85 days post-treatment. One patient developed skin ulceration, likely due to dermal rather than mid-subcutaneous injection, and 2.3% (6/258) developed temporary dysphagia due to postinjection swelling and pain.

Despite submental fat reduction, increased skin laxity has not routinely been observed. Paradoxically, 92.7% of patients in the REFINE-1 trial reported no change or improvement in submental skin laxity, possibly due to neocollagenesis [12].

No systemic adverse effects have been reported following subcutaneous injection of DCA, despite documented rapid absorption and transient increases in plasma levels of endogenous DCA 12 to 24 hours after injection. In 2 Phase I clinical trials, there were no meaningful differences in heart rate, plasma concentration of lipids, proinflammatory cytokines, liver transaminases or creatinine levels [16,17]. A separate Phase

I study demonstrated no changes in QT intervals or other electrocardiogram parameters following subcutaneous administration of ATX-101 [1].

Of note, in a later study in which more male patients were included, 8 of 39 men experienced mild transient alopecia in the area of treatment. This resolved in all patients by the 6-week follow-up [19].

CRYOLIPOLYSIS

Preoperative Planning

Similar to DCA, cryolipolysis is used to target preplatysmal fat. Therefore, a thorough physical examination of the submental region should be performed to rule out other causes of submental fullness. The presence of adequate preplatysmal fat deposition should be confirmed via palpation. As described in the “Preoperative planning” section for DCA, complete knowledge of relevant anatomy is necessary before use of cryolipolysis in the submental region.

Preparation/Procedural Approach

The CoolMini vacuum cup attachment has a concave contour to fit the neck and measures 2.5×7.5 cm at the opening (Fig. 8). A lubricant gel must be applied to the skin before placing the applicator on the skin. A new disposable gel trap must be used each session to prevent gel from being suctioned into the vacuum line. Once the applicator is in place, vacuum suction is initiated, which draws the redundant tissue into the

treatment applicator. The treatment session is then initiated, and a preset cooling temperature is achieved and sustained within the treatment time period. Support straps are then attached from the vacuum head to a support pillow to secure the applicator in place and increase patient comfort.

Kilmer and colleagues [19] described their treatment method in which 1 treatment session per visit was delivered for a total of 60 minutes at -10° Celsius. One to 2 treatment sessions total were delivered 6 weeks apart. The applicator was applied to the central submental region for 1 treatment window.

More recently, Bernstein and Bloom [26] described a different treatment method with 2 overlapping treatment sessions in the same day. This was designed to treat a larger surface area with 20% overlap in the center of the neck. The 2 consecutive treatment sessions were delivered on each side of the submental region at -11° Celsius for 45 minutes each. The 2 treatment 7.5×2.5 -cm areas were marked before onset by placing the patient’s head in neutral position, then drawing the parallel treatment windows to have 20% overlap centrally.

Immediate Postprocedural Care

At treatment conclusion, the submental tissue treated is firm and cold to touch. The patient should be counseled to expect erythema, edema, and possible purpura. There is typically a notable “butter stick” deformity of elevated, edematous tissue when the applicator is removed [27]. Manual massage for 2 minutes to rewarm

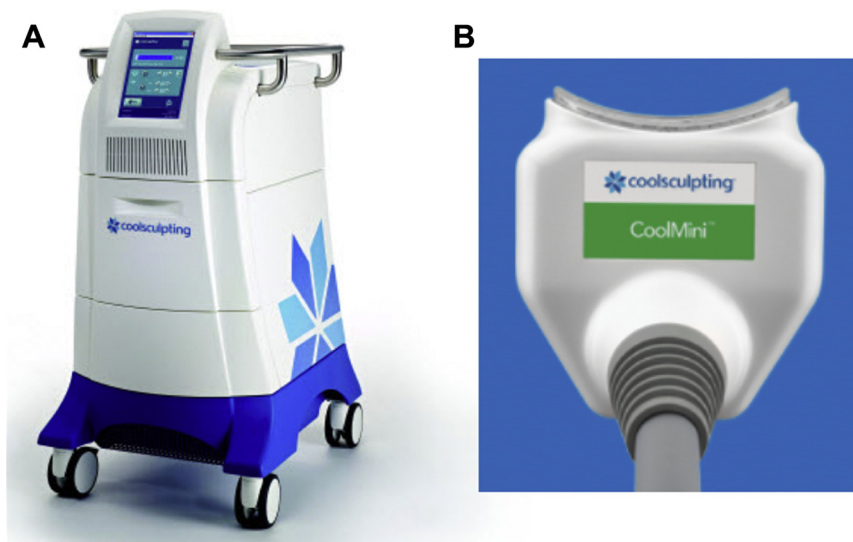


FIG. 8 Coolsculpting device (A) and CoolMini applicator (B). (Images from ZELTIQ Aesthetics, Inc, Pleasanton, CA.)

the tissue is recommended immediately posttreatment [19]. Boey and Wasilenchuk [28] reported greater mean tissue reduction in patients receiving massage immediately posttreatment on the abdomen, possibly due to an increase in reperfusion injury with massage that may stimulate additional adipocyte damage [29].

Rehabilitation and Recovery

Following treatment, most patients (58/60 in 1 study) develop immediate purpura. Most patients also experience some degree of edema and erythema. This usually resolves within 1 week of treatment. Of 60 patients treated in the original pilot study, only 3 had mild swelling 1 week posttreatment. The predominant symptom at this time was numbness in 50% of patients, as well as tingling in 20%. These symptoms had resolved in all patients at 12-week follow-up. Other less common adverse effects included temporary sensitivity, itching, and tenderness. One patient developed transient hyperpigmentation that had resolved by 27 days [19].

Clinical Results in the Literature

Kilmer and colleagues [19] examined the efficacy of the CoolMini applicator with a multicenter, prospective, open-label, nonrandomized interventional cohort study that included 60 patients. Subjects received two 60-minute treatment sessions, 6 weeks apart. One of the 59 patients received only 1 treatment. Overall, 3 blinded independent physician reviewers were able to correctly identify 91.4% of pretreatment and post-treatment images, indicating effective and significant

reduction in submental fullness. Secondary endpoints included patient satisfaction questionnaires and reduction in submental fat thickness on ultrasound examination at 12 weeks posttreatment. Mean fat reduction among patients was 2 mm, which was statistically significant ($P < .0001$) and corresponded to an overall 20% reduction in fullness. When surveyed, 76% of patients found the treatment comfortable, and 88% stated that they would recommend the treatment to a friend.

Bernstein and Bloom [26] more recently reported a new approach as described previously in which 2 overlapping treatment sessions were applied to the neck over 45 minutes each in 14 total subjects. Twelve patients then received a second identical bilateral treatment session; however, 2 patients at follow-up were deemed to have insufficient residual fullness for overlapping treatments and instead received a central, single treatment session. Skinfold caliper measurements at 12 weeks after final treatment showed a mean fat layer reduction of 2.3 mm ($P < .001$). In addition, 3-dimensional imaging showed a mean reduction of 3.77 mm ($P < .001$). Patient surveys showed that 93% of patients treated were satisfied and would recommend the treatment to a friend. Results from cryolipolysis treatment are demonstrated in Fig. 9.

Potential Complications/Risks/Benefits/Limits

Cryolipolysis provides a safe and noninvasive alternative for submental fat reduction without significant downtime. Patients with excess skin laxity or platysmal banding may not be ideal candidates, as it may

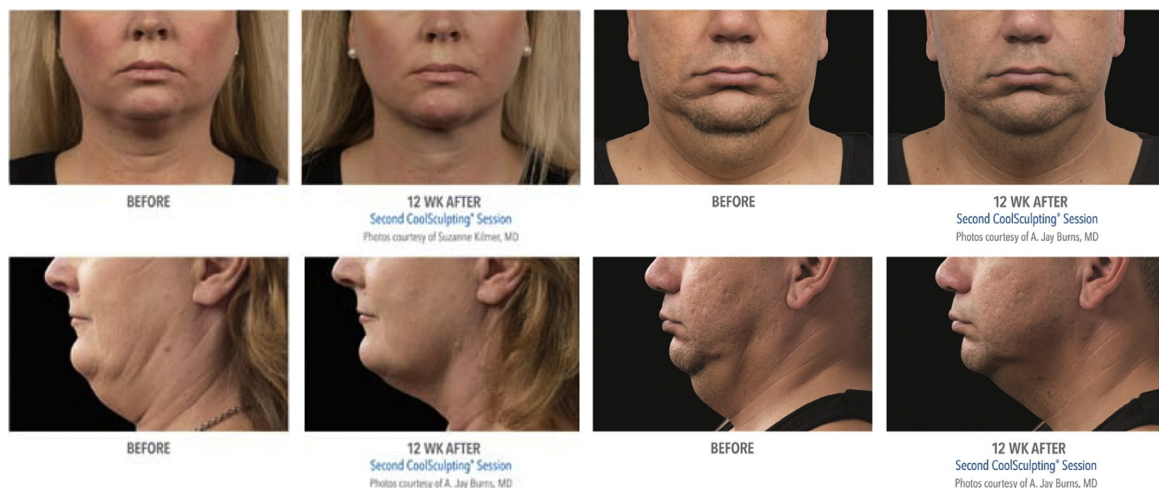


FIG. 9 Pretreatment and posttreatment results following 2 sessions of CoolMini. (Images from ZELTIQ Aesthetics, Inc, Pleasanton, CA.)

accentuate these issues. Patients should be counseled to expect 1 to 2 treatment sessions, at least 6 weeks apart. Select patients may benefit from more than 2 treatment sessions, contingent on response and tolerability.

All listed side effects were temporary, with no serious long-term adverse events thus far reported. There have been reports of paradoxical adipose hyperplasia following cryolipolysis on the lower body; however, this has not yet been reported in the submental region. This has been hypothesized to be due to reactive fibrosis and septal thickening, which leads to hypoxia of adipose tissue and resultant adipose hyperplasia [29]. No systemic adverse effects have been reported. Klein and colleagues [30] found no associated changes in serum lipid or liver enzyme levels following cryolipolysis on the flank. Despite lack of nerve paralysis during clinical trials, a rare report of marginal nerve injury following use of cryolipolysis in the submental region is in press by Dr Jeffrey Dover's group.

It is important to note that device interference can occur when the vacuum cup sensors detect an unexpected change in temperature, which triggers the device to discontinue the treatment cycle. This can be caused by patient movement, electrical noise, or condensation [19]. If the treatment session stops prematurely and the vacuum suction is disabled, to restart the session a new disposable gel trap must be used to reinitiate suction. If this happens, the use of an additional disposable gel trap applicator will result in increased consumable costs. The patient must be instructed to remain motionless and not speak during the treatment cycle. Therefore, comfort should be ensured before treatment initiation. The strap to secure the vacuum applicator, when applied properly, assists in preventing device interference.

Overall, the device is easy to operate and requires minimal physician face-time during treatment. In contrast to other injectable or surgical treatments, this offers the advantage of performing other duties while simultaneously using this therapy. If an office is already using cryolipolysis for other treatment areas, the CoolMini applicator can be purchased at an additional cost. It is important to consider that the area of treatment is limited to the size of the applicator (which is an in-office consumable), and injectable alternatives can offer more control and customization of both dosing and the treatment area.

ULTRASOUND AND RADIOFREQUENCY DEVICES

Ultrasound treatment for skin tightening of the lower face and neck (Ulthera, Inc, Mesa, AZ) uses microfocused ultrasound with visualization. This

technology penetrates to a depth of up to 5 mm beneath the skin to induce neocollagenesis within the dermis and superficial musculoaponeurotic system [31]. However, the effect of this modality on adipose tissue has not been well established. This procedure has traditionally been marketed for skin tightening and has not been demonstrated to eliminate preplatysmal fat deposition.

There have been reports of high-intensity focused ultrasound devices being used to treat unwanted adipose tissue through selective heating and coagulative necrosis of subcutaneous fat on the flank and abdomen [32,33]. These areas were treated at a depth of greater than 1 cm of adipose tissue, which is often not present in the submental region. To the authors' knowledge, this method of fat reduction has not been studied in the submental region. An alternative method of nonthermal focused ultrasound (UltraShape; Syneron Medical Ltd, Yokneam, Israel) uses mechanical energy to cause cavitation and fat cell lysis without significant elevation in tissue temperature. This in theory allows more selective destruction of adipocytes than tissue heating, without damaging surrounding structures such as blood vessels, lymphatic vessels, connective tissue, nerves, or muscle [34]. Again, studies of this technology for fat reduction at this time are limited to non-head and neck sites. Therefore, there are currently no ultrasound devices on the market specifically marketed to treat submental fat deposits.

Various radiofrequency devices are currently available to address laxity within the head and neck region [35]. None of these devices have been shown to target adipose tissue. For more in-depth review of both ultrasonic and radiofrequency modalities, please refer to Neil Sadick's article, "Non-Surgical Skin Tightening (Moving Below the Neck - Breast Lifting, Arm Lifting)," in this issue.

SUMMARY/DISCUSSION

Noninvasive treatment of submental fullness is a relatively new but commonly sought-after treatment within the field of cosmetic medicine. A recent 2016 survey by the American Society for Dermatologic surgery indicates that there has been a 2.5 times increase in the number of body-contouring procedures performed by physician members, including more than 177,000 cryolipolysis cases and 37,000 Kybella procedures [36]. The American Society for Aesthetic Plastic Surgery reported a total of 169,695 nonsurgical fat reduction procedures performed by members in 2016 [37]. Clinicians performing cosmetic procedures will therefore benefit from knowledge and utilization of noninvasive modalities to treat

TABLE 3
Treatment Recommendations for Multimodal Approach to Neck Rejuvenation

	Same Day Option 1	Same Day Option 2	Same Day Option 3
Brown spots and macular seborrheic keratoses	1. IPL 2. QS 532,694,755 nm a. 755 nm b. $\pm$ dual 1927	1. QS 532,694,755 nm 2. 1927 nm	
Dyschromia and superficial crepiness	1. IPL 2. QS 532,694,755 nm 3. Nonablative fractionated laser (1440,1550,1565 nm) a. Dual 1927 b. Series of 3 nonablative fractionated 1550 nm or series of 5 nonablative fractionated 1440 nm every 2 wk	1. IPL 2. QS 532,694,755 nm 3. Ablative fractionated laser (10,600 nm CO₂)	1. IPL 2. MFU-V 3. QS 532,694,755 nm
Dyschromia, crepiness, and laxity	1. IPL 2. QS 532,694,755 nm 3. MFU-V or MRF (externally or internally applied) 4. Ablative fractionated laser (10,600 nm, CO₂) a. Dual 1927 b. Nonablative fractionated 1550 nm (1 mo post dual) or series of 5 nonablative fractionated 1440 nm every 2 wk c. MFU-V		
Dyschromia and mild submental fat, no laxity	1. IPL 2. QS 532,694,755 nm 3. Deoxycholate serial injections every 6–8 wk a. Dual 1927, Series of 1440 $\times$ 5 b. Deoxycholate serial injections every 6–8 wk	1. IPL 2. QS 532,694,755 nm 3. Liposculpture a. Dual 1927 b. Submental liposuction	
Dyschromia and mild submental fat with laxity	1. IPL 2. QS 532,694,755 nm 3. Deoxycholate serial injections every 6–8 wk 4. MFU-V 4 wk after last deoxycholate Injection a. Dual 1927, 1927 series of 5 nonablative fractionated 1440 nm b. Deoxycholate serial injections every 6–8 wk c. MFU-V	1. IPL 2. QS 532,694,755 nm 3. Subsurface MRF with Microlipo a. Dual 1927 b. Submental liposuction c. MFU-V (1 mo after liposuction)	1. IPL 2. QS 532,694,755 nm 3. Laserlipolysis

(continued on next page)

TABLE 3
(continued)

	Same Day Option 1	Same Day Option 2	Same Day Option 3
Dyschromia and moderate to severe submental fat, no laxity	1. IPL 2. QS 532,694,755 nm 3. Liposculpture a. Dual 1927 b. Submental liposuction	1. IPL 2. QS 532,694,755 nm 3. Mini cryolipolysis: repeat second treatment in 4 wk a. Dual 1927 b. Deoxycholate serial injections every 6–8 wk	
Dyschromia and moderate to severe submental fat with laxity	1. IPL 2. QS 532,694,755 nm 3. Laserlipolysis a. Dual 1927 b. Submental liposuction c. MFU-V (4 wk after liposuction)	1. IPL 2. QS 532,694,755 nm 3. Mini cryolipolysis: repeat second treatment in 4 wk 4. MFU-V a. Referral for facial rhytidectomy	
Horizontal neck lines	1. Neuromodulators 2. Dilute HA a. Dilute HA (highly cohesive HA mixed 1:1) b. Nonablative fractionated 1550/1440 nm or Neuromodulator (1 wk before laser)		

Treatment options by Dr Sabrina Fabi listed by numbers. Treatment options by Dr Sue Ellen Cox listed by letters.

Abbreviations: HA, hyaluronic acid; IPL, intense pulsed light; MFU-V, microfocused ultrasound with visualization; MRF, monopolar radiofrequency; QS, Q-switch.

From Vanaman M, Fabi SG, Cox SE. Neck rejuvenation using a combination approach: our experience and a review of the literature. *Dermatol Surg* 2016;42:S98–99; with permission.

submental fullness. These noninvasive alternatives offer the benefit of a quicker outpatient procedure with relatively minimal downtime. Popularity of both injectable DCA and cryolipolysis will likely only increase in coming years as further long-term data become available.

It is relevant to mention that the use of Kybella is now being studied beyond the treatment area described in this article. Off-label treatment has been extended to the lateral neck and jowls. This is an area of potential future use.

When comparing the 2 modalities, cryolipolysis has less downtime and potential adverse effects overall. More edema, erythema, induration, and pain should be expected after DCA injection, which can require days to weeks of recovery. Therefore, in the authors' experience, if the size of the treatment area is amenable to the vacuum cup applicator of CoolMini, this is the preferred method. Additionally, up to 2 sessions of cryolipolysis are typically required versus 2 to 4 with DCA. However, for very small or very large areas of submental fat or asymmetrical

adipose hyperplasia, DCA injections offer a more tailored, targeted treatment approach. If both modalities are offered, a thorough discussion of both options should be had with the patient. One option is also to first treat with cryolipolysis, followed by focal injection of DCA to residual areas of fullness. As studies of DCA for areas outside of the submental area are completed, this may change how treatments are planned and guided.

It is important to consider all factors that create an aged appearance in the neck region. Treatment of neck fullness may often require accompaniment of other modalities to address issues such as laxity and photoaging of skin, rhytides, and prominent platysmal bands. Each problem can be addressed with a variety of therapeutic modalities, which may be used in conjunction to restore an overall youthful appearance to this region [1]. The use of ultrasound, radiofrequency, or fractionated laser treatments in addition to injectable DCA or cryolipolysis may provide a more global noninvasive approach to the aging neck. A guide to a multifaceted

approach to target numerous concerns can be reviewed in Table 3. Both modalities discussed in this article may be used before or in conjunction with other skin tightening or resurfacing devices. It is also important when planning therapy to keep in mind that both cryolipolysis and Kybella may require multiple/serial treatments, which can come at significant patient cost. Depending on the number of treatments required, other more invasive methods may be more practical and cost-effective to address multiple concerns.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.yacs.2018.02.005>.

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Nonsurgical Skin Tightening

Moving Below the Neck: Breast Lifting, Arm Lifting



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KEYWORDS

• Fillers • Radiofrequency • Ultrasound • Lasers • Shockwaves • Light • Combination

KEY POINTS

- Modern technologies and new-generation fillers are heavily used to achieve nonsurgical skin tightening of the body.
- Energy from ultrasound, radiofrequency, laser, and shockwaves are the main sources integrated in skin-tightening devices.
- Combination approaches, maintenance regimes, and appropriate patient selection are key to successful results.

INTRODUCTION

Noninvasive skin-tightening procedures have overwhelmingly increased in popularity over the years due to technological innovations and scientific methodologies that are able to deliver clinical outcomes with minimal side effects and virtually no downtime. Skin-tightening treatments can be done not only in the face but in other areas of the body. Most commonly patients request improvement of laxity in the neck, décolletage, arms, abdomen, thighs, and knees. Several technologies have been enlisted in reduction of excess skin and these are frequently paired with noninvasive fat-reduction procedures. Ultrasound, lasers, radiofrequency (RF), and shockwaves spearhead the devices dermatologists use, although lately new-generation volumetric fillers have demonstrated favorable results for nonfacial skin tightening.

ENERGY-BASED DEVICES FOR SKIN TIGHTENING

Radiofrequency

RF devices have a leading role in improving skin laxity in all areas of the body. Their mechanism is based on delivering RF waves to the tissue layers, generating thermal energy that triggers a cascade of events including collagen contraction, coagulation, matrix remodeling, and ultimately increased dermal thickness. As RF energy is not absorbed by chromophores, devices can be used in all skin types. The first generation of devices had drawbacks for the patients, such as excess pain, but newer-generation devices have cooling systems or different electrode organization that delivers heat homogeneously for increased efficiency and patient comfort. Side effects after RF treatment included transient erythema or bruising, which is

Disclosure Statement: Nothing to disclose.

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self-resolving. Depending on the number of electrodes, RF can be classified into unipolar, bipolar, multipolar, or fractional devices. Unipolar devices have a single electrode with a grounding pad, and achieve bulk heating with deep tissue penetration, whereas bipolar devices consist of 2 electrodes that emit a fast, alternating current. Combining RF energy with other sources of energy, such as laser/light, ultrasound, or pulsed electromagnetic fields, has been used in devices these past couple of years (Exilis, BLT, USA or Venus Legacy, Venus Concept, Toronto) to maximize the synergy, and thus clinical efficacy of devices on skin laxity. Other types of RF devices have several generators rather than electrodes (Endymed3DEEP, NYC, NY) that increase their capacity to penetrate deep tissue across a larger anatomic area. Fractional RF, such as microneedling RF or nanofractional RF, are also used for skin tightening, particularly in small delicate areas. These devices create thermal and mechanical micro-wounds that stimulate coagulation and remodeling, and although they can rejuvenate fine lines and wrinkles, they are more regularly used to treat striae, scarring, and textural concerns. A minimally invasive RF device that uses an internal probe to deliver RF energy to the target tissue, while continuously monitoring temperature, is the latest RF device to enter the skin-tightening field (ThermiRF; Thermi Aesthetics, Irving, TX). As opposed to the other devices that typically require a series of 3 to 6 treatments at monthly intervals to have measurable results, this temperature-controlled RF device treatment is done once, and results have been demonstrated to be durable.

Ultrasound

Microfocused ultrasound (MFU) devices are also popular for noninvasive skin tightening. As opposed to high-intensity ultrasound, mainly used for fat reduction, MFU devices deliver focused ultrasound waves to the dermal and subcutaneous layers (up to 5 mm), that induce thermal coagulation, triggering an inflammatory cascade that leads to fibroblast activation and collagen/elastin production. The main device used in the United States is Ulthera (Merz, Raleigh, NC) that combines MFU with high-resolution ultrasound imaging (MFU-V), to enable visualizing tissue planes to a depth of 8 mm and allow treatment control. Although this device has been used off-label in several anatomic areas, it has recently been approved by the Food and Drug Administration for treating the neck and chest. Typically, 1 to 2 treatments are necessary and side effects are minimal and self-resolving.

Lasers

Laser and light devices were the first technologies to be evaluated for skin tightening. Nonablative laser and broadband light devices with reduced downtime and adverse effects and wavelengths from 532 to 1927 nm have been mainstreamed in use over ablative treatments for improving laxity. Both broadband light and nonablative lasers deliver thermal energy in the lower levels of the dermis, stimulating a wound-healing response that leads to increased collagen production while leaving the epidermis intact. Clinical studies have shown that combination of 532 nm/1064 nm devices stimulate collagen production, an effect that lasts 6 to 12 months after treatment. The most commonly used broadband device for skin tightening is the Titan system by Cutera (Cutera, Inc, Brisbane, CA) that uses broad-spectrum infrared light to bulk heat the dermis up to 3 mm deep. This device has been shown to be safe and effective in all skin types, and results are evident after 1 to 2 monthly sessions. Skin tightening using laser/light devices has been applied predominantly in the facial area rather than the body, so in the authors' experience, it would not be a first-choice device to treat off-face laxity.

Shockwaves

Shockwave devices deliver high-pressure pulses to the tissue in ultra-short intervals that produce mechanical pressure waves promoting cavitation and localized increase in tissue temperature. The combination of acoustic energy with thermal stimulates the wound-healing response, and matrix remodeling resulting in collagen/elastic production and improvement of laxity. Shockwave device applicators can deliver either focal or radial waves, the former being more intense targeted to the tissue, whereas the latter can be more superficial and diverge over the treatment area. Treatment by shockwave devices is generally well tolerated, and even pleasant for some patients, and a self-resolving redness in the treated area is the only reported side effect thus far. Although not excessively used in aesthetic dermatology for noninvasive skin tightening, positive results have been demonstrated when using these devices to treat cellulite, as well as in combination with fat-reduction procedures, such as liposuction.

New-Generation Fillers

A new trend in noninvasive skin tightening for the body is the use of new-generation fillers. Although only calcium hydroxylapatite (CaHA) has been approved for off-face sites (the hands), several physicians have used poly-L-lactic acid (PLLA) in areas such as the abdomen,

arms, décolletage, and gluteal region. Aside from skin laxity, fillers with biostimulatory properties induce a tissue response that triggers tissue remodeling, collagen production leading to improved skin quality, and increased dermal thickness. Depending on the region, 2 to 3 treatments are typically necessary, but there is no downtime, and improvement continues over time. Whether a physician selects a filler over an energy-based device when treating patients for noninvasive off-face laxity depends on several parameters, such as the severity of laxity, prior treatment experiences, and the patient's financial capacities.

NONINVASIVE SKIN TIGHTENING OF THE BODY

Neck

Excess laxity in the neck area is a common concern nowadays, particularly when it is in contrast with a smooth facial appearance. Historically, neck laxity was treated surgically with a necklift; however, nowadays noninvasive or minimally invasive procedures have been developed to provide nonsurgical approaches for cervicofacial rejuvenation. Microfocused ultrasound and radiofrequency devices are the 2 devices commonly used for improving neck laxity, although use of a diode laser for this indication also has been reported (Fig. 1) [1–3]. A recent clinical study

comparing the efficacy and safety of temperature-controlled RF and MFU-V for the lifting and tightening of neck demonstrated comparable efficacy and lack of side effects with both devices. In the study, 20 subjects aged from 18 to 65 with moderate neck skin laxity were randomized to receive either 1 treatment of RF or MFU-V. Both RF and MFU-V led to a significant decrease in the mean investigator-assessed Neck Laxity Grade by day 90 and persisted to day 180. Subject assessment of firmness, texture, and laxity also significantly improved in the same time frame [4]. The use of subdermal monopolar RF has emerged as a safe and effective means for treating the aging neck. It has significant advantages over other aesthetic devices, as it provides the triad benefit of disrupting fat volume and superficial musculoaponeurotic system, and skin tightening of the face, neck, and jawline. For suitable patients, this treatment can be used to achieve significant aesthetic improvements of the aging neck. Finally, during a panel of 11 expert physicians assigned to arrive at a consensus on the best current practice for submental skin tightening and contour improvement, subdermal monopolar RF was shown to represent the most effective means for disrupting fat volume and skin tightening of the face, neck, and jawline in suitable patients [5]. Despite the plethora of articles on RF and MFU for neck laxity, there are few reports on the use of lasers for neck skin tightening. In a retrospective,



FIG. 1 A 64-year-old woman before (left) and after 3 months (right) of MFU. (Courtesy of Neil Sadick, MD, Buffalo, NY.)

cross-sectional study of 17 patients, treatment with a 975-nm diode laser to correct deformities in the cervicofacial region showed a significant skin tightening effect in all patients 3 months after the procedure [6]. Finally, a report using CaHA filler for neck skin tightening was published, but there is no previous precedent for using fillers in the area. In this study, 20 subjects with skin laxity in the neck and décolletage received multiple, linear, subdermal injections of CaHA diluted with preserved saline. Immunohistochemical analysis of biopsy tissue demonstrated significant collagen increase at 4 months, and investigator and patient satisfaction was high [7].

Decollete Area

The skin in the chest/decollete area has a thin epidermis, and decreased number of pilosebaceous units, thus can have an excessively lax/dry appearance with age. Tightening that area has increased in popularity and can be achieved with volumetric fillers, such as PLLA or energy-based devices (lasers, RF, MFU) [8]. A combination approach also serves most patients best, as using high fluences and densities with monotherapy is not recommended due to prolonged erythema, scarring, and depigmentation. A multimodal approach with multiple technologies to obtain safe, successful, and sustained improvement of the synergistic effects of various therapies leads to superior clinical results [9]. MFU therapy is the first choice of treatments, as it creates minute areas of coagulation at discrete depths of 1.5, 3.0, or 4.5 mm, leading to neocollagenesis and tissue contraction in the reticular dermis and subdermis. An original study of 24 subjects receiving MFU for chest laxity showed a 1-point to 2-point improvement at days 90 and 180, respectively. All subjects were satisfied or very satisfied at day 90, with similar results at day 180 [10]. Similar results were observed in a follow-up study in which 125

patients with deep to very deep lines and folds on the chest received MFU treatment using all 3 transducers of 1.5-mm, 3.0-mm, and 4.5-mm depth and 280 lines per treatment. A blinded investigator noted improvement in 69.9% and 66.4% of subjects at 3-month and 6-month follow-up, respectively [11]. Injectable PLLA is another minimally invasive approach to improve skin laxity in the décollete area and is often used together with MFU [12,13]. Due to its biostimulatory properties, injection of PLLA not only provides immediate volumization, but also continuous neocollagenesis that improves skin quality and laxity over time. In a recent study in which 25 women with moderate-to-severe crepiness and wrinkling of the décolletage were injected with 1 vial of PLLA at each of 3 treatments, there was 83% improvement according to investigator ratings at the 3-month follow-up [13]. Typically for lines and rhytides together with loss of volume, a combination of injectable filler with MFU or RF is recommended, whereas nonablative lasers are included in the treatment strategy in cases in which pigmentation is also present.

Arms

Arms laxity is another area of concern, particularly after fat-reduction procedures, such as cryolipolysis or liposuction. For this reason, typically combination approaches are recommended, such as liposuction paired with RF, or even energy-assisted liposuction (Fig. 2) [14–16]. Minimally invasive devices can injectable fillers can offer some improvement in laxity, particularly the latest generation of temperature-controlled RF. In an open-label clinical trial involving 12 subjects with moderate-to-severe skin laxity in the posterior upper arms treated with temperature-controlled RF, significant improvements in skin laxity were observed at both day 30 and at day 90 posttreatment as assessed by the non-treating investigator. Most subjects were “satisfied” to

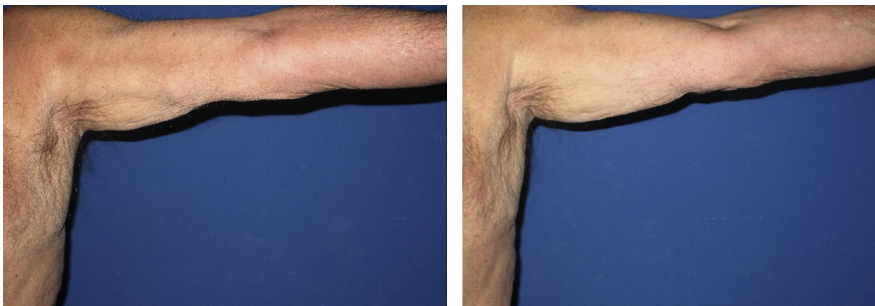


FIG. 2 A 70-year-old man before (*left*) and 6 months after (*right*) 1 treatment of PLLA. (Courtesy of Dr Suleima Arruda, New York City, NY.)

“extremely satisfied” with their results [17]. Fillers such as PLLA and CaHA also have been used for treating arm laxity [12]. In a recent study using CaHA in the upper arms of 10 women, the filler was diluted 1:2 with normal saline solution and 2% lidocaine was injected subdermally using a short, linear-threading technique. Diluted CaHA resulted in an overall increase in dermal thickness of 26.7% ($P \leq .05$). In both case series, 90% of subjects and physicians rated treatment outcomes on GAIS (Global Aesthetic Improvement Scale) as much or very much improved. Treatment was well tolerated [18].

Abdomen

Similar to the arms, the abdominal and flank area can present excess laxity, particularly after life events such as childbirth or weight loss, or after fat-reduction procedures such as cryolipolysis or liposuction. Several generations of RF have been traditionally used for this indication, or broadband light [19], but recently temperature-controlled RF and injectable fillers have been the main first-choice treatments. In an original study by Key and colleagues [20], 14 subjects presenting with abdominal laxity were treated up to 4 times using the transcutaneous monopolar RF device at 1 or 2 zones in the abdominal region. Average rated improvement was 0.75 and 0.80 for graders 1 and 2, respectively, whereas patients perceived tightening of 2.14 points on a 0 to 4 scale (0 = lowest tightening result, 4 = highest tightening) [20]. In another study, using an RF device that combined infrared light and vacuum, 20 women received 5 monthly treatments to the abdomen. Significant ($P < .02$) improvement in skin laxity and tightening was noted by both the physician and patients. Treatments were well tolerated with no major safety concerns (1 purpura, 1 mild burn) [21]. Injectable fillers, such as PLLA, have been increasingly used for improving laxity [22], and experimentation with filler, such as CaHA, for this purpose has also commenced [18]. Reports of acoustic wave therapy, particularly after liposuction, have been reported to improve skin laxity, as the cavitation pressure waves stimulate dermal fibroblasts to produce excess collagen and infiltrate the area with growth factors that provide synergistic rejuvenation [23].

Knees

Sagging skin in the knee area is a common aesthetic concern, and minimally invasive energy-devices such as MFU have been shown to improve knee laxity [24]. In a clinical study including 30 adult women with

mild to moderate bilateral skin laxity above the knees, MFU-V (4 MHz, 4.5 mm followed by a 7-MHz, 3.0-mm transducer, 480 lines) was applied to a grid of eight 25-mm² squares above each knee. Among 28 evaluable subjects, 24 subjects (86%) showed improved lifting and tightening of knee skin laxity at 90- and 180-day follow-up visit, and there were no adverse events or evidence of skin injury [25].

SUMMARY

Energy-based technologies together with fillers have been demonstrated to safely and effectively improve skin laxity in off-face sites with no downtime or side effects. Combining these treatments with procedures that target chromophores to even tone, fillers to replete volume, devices to reduce fat, and a skincare regimen that offers sun protection is key to preventing aging, securing a natural healthy look in the scope of whole body rejuvenation.

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Rejuvenation of the Neck



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KEYWORDS

• Neck rejuvenation • Neck lift • Platysmaplasty • Platysma plication • Submental incision

KEY POINTS

- Signs of neck aging can occur due to a combination of retaining ligament attenuation and platysmal muscle banding, skin excess and loss of elasticity, excess preplatysmal and subplatysmal fat, submandibular gland hypertrophy/ptosis, and digastric muscle hypertrophy.
- Surgical management can consist of a combination of different access approaches and internal procedures, including fat excision (preplatysmal and/or subplatysmal fat), medial or lateral platysmaplasty, and submandibular gland and digastric muscle partial excision.
- Treatment must be individually tailored based on preoperative examination and discussion with patients to identify their concerns and goals of treatment.
- The face must be evaluated as a whole. Patients often benefit from other ancillary procedures to achieve harmonious rejuvenation of the face.

INTRODUCTION

Signs of neck aging can occur as early as the late 30s. Successful correction of these deformities requires a global evaluation of facial aesthetics, because neck rejuvenation is often performed in conjunction with rhytidectomy and other ancillary procedures, such as genioplasty, to achieve a harmonious surgical outcome. There are multiple surgical and nonsurgical methods to address the neck—thorough evaluation and discussion of a patient's goals helps determine the preferred intervention.

- The youthful neck is characterized by a distinct mandibular border, a cervicomenal angle of 105° to 120°, a visible anterior border of the sternocleidomastoid muscle (SCM), a slight subhyoid depression, slightly visible thyroid cartilage, and the relative absence of jowls (Fig. 1) [1,2].
- It is critical to assess the position of the soft tissue pogonion, because this imparts a substantial

cosmetic effect of the appearance of the neck and facial profile (Fig. 2). A retropositioned pogonion is usually associated with a class 2 occlusal relationship and contributes to an aged appearance and obtuse cervicomenal angle.

RELEVANT ANATOMY

Knowledge of the local anatomy allows a surgeon to safely address the culprits of a patient's aesthetic concerns.

- From superficial to deep, the tissue planes include skin, subcutaneous or preplatysmal fat, platysma muscle, subplatysmal fat, deep cervical fascia, and the underlying digastric muscles and submandibular glands.
- The superficial muscular aponeurotic system (SMAS) and platysma muscle are in continuity, permitting neck rejuvenation and platysma tightening via rhytidectomy techniques that reposition the SMAS [3,4].

The authors have nothing to disclose.

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FIG. 1 Profile view demonstrating youthful features of the neck. 1, Defined inferior mandibular border; 2, hyoid depression; 3, visible anterior border of the SCM; and 4, cervicomental angle between 105° and 120° . (From Coleman SR, Saboeiro AP. Structural fat grafting. In: Neligan P, editor. Plastic surgery, vol 2. 4th edition. Philadelphia: Elsevier; 2012. p. 312; with permission.)

- Cervical retaining ligaments anchor the platysma to the deep fascia of the neck [5]. These are located along the anterior border of the SCM, between posterosuperior edge of the platysma and the mandibular angle and at the inferomedial border of the parotid gland/posterior submandibular gland. Furthermore, the platysma muscle has a horizontal osseous insertion along the medial mandibular body known as the mandibular septum, which contributes to jowl formation with aging [6].
- The digastric muscle is composed of 2 separate muscle bellies. The anterior belly originates from the parasymphseal inferior border of the mandible and is innervated by the mandibular division of the trigeminal nerve. The posterior belly originates from the mastoid notch of the temporal bone and is innervated by the facial nerve. The anterior and posterior

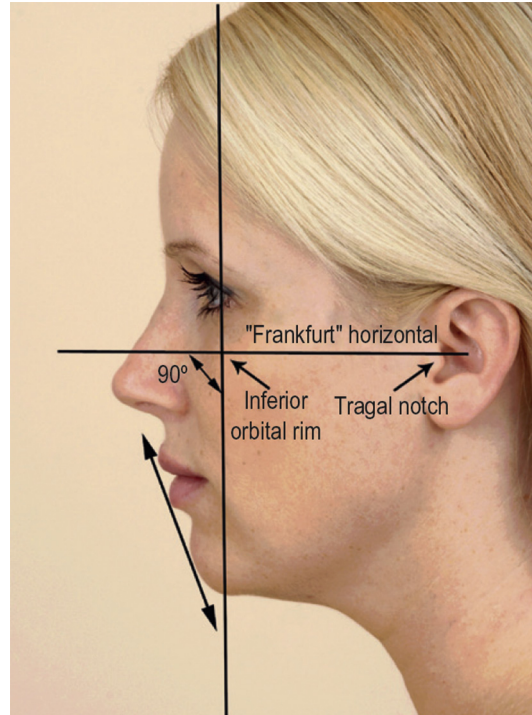


FIG. 2 Ideal lip and chin relationship on profile view: Riedel line. The chin position should fall on a line that connects the most projecting aspects of the upper and lower lip. (From Coleman SR, Saboeiro AP. Structural fat grafting. In: Neligan P, editor. Plastic surgery, vol 2. 4th edition. Philadelphia: Elsevier; 2012. p. 317; with permission.)

bellies meet via the intermediate tendon that inserts onto the hyoid bone. The 2 bellies of the digastric muscle, along with the inferior border of the mandibular body superiorly, form the submandibular triangle (Fig. 3).

- The facial vessels cross the submandibular triangle in the subplatysmal plane. The marginal mandibular nerve (MMN) also passes in this area, superficial to the facial vessels along the inferior border of the mandible [7], and is prone to injury with neck rejuvenation.
- The submandibular gland is composed of a superficial and deep lobe, with the MMN coursing superficial and along the cephalad aspect of the submandibular gland capsule [8]. When indicated, the superficial submandibular gland can be partially resected by incising the inferomedial capsule to avoid the MMN. Care must be taken to control supplying vascular branches from the facial or lingual vessels [8].

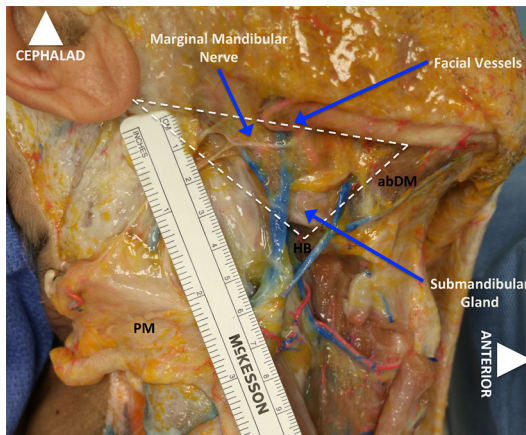


FIG. 3 Submandibular triangle anatomy. The submandibular triangle is defined superiorly by the inferior mandibular border, anteriorly by the anterior belly of the digastric muscle (abDM), and posteriorly by the posterior belly of the digastric muscle (*dotted white lines*). The facial vessels, MMN, and submandibular gland can be located with this area. The platysma muscle (PM) is reflected posterolaterally. HB, hyoid bone. Note that the MMN crosses the cephalad aspect of the submandibular gland.

THE AGED NECK

The aged neck is manifested by retaining ligament attenuation, resulting in platysma edge shortening and banding. Furthermore, skin laxity, preplatysmal or subplatysmal fat excess, digastric muscle hypertrophy, and hypertrophied and/or ptotic submandibular glands contribute to the appearance of an aged neck (Fig. 4). Treatment options vary depending on individualized patient evaluation and discussion a patient's treatment goals.

SURGICAL TECHNIQUE

Preoperative Planning

- A thorough patient history and physical examination are performed, with particular attention to a history of hypertension and nicotine product use. If present, hypertension must be medically controlled prior to surgery. Surgery is avoided in nicotine product users due to the risk of skin flap necrosis.
- Standardized medical photographs are obtained. These are invaluable for patient counseling, assessment of postoperative results, surgeon self-reflection for surgical technique improvement, and medicolegal reasons.
- Ideal candidates for isolated neck surgery are patients who desire neck rejuvenation without the need to concomitantly address the midface with a facelift.

- It is critical to evaluate a patient's goals and expectations and reconcile these with the surgeon's goals and the expected results of the varying intervention options.
- Total facial analysis is paramount. Isolated neck procedures do not address the jowls - patients with jowls are best served by a concomitant facelift. Furthermore, it is important to discuss relevant procedures that may enhance the result of neck surgery, including chin augmentation, buccal fat pad removal, and skin resurfacing [9,10].
- Systematic neck evaluation is critical to determine appropriate intervention and includes assessment of
 - Skin texture, elasticity, and laxity
 - Preplatysmal and/or subplatysmal adiposity. A pinch test is used and the patient is asked to grimace. Preplatysmal fat tends to remain within the examiners fingers whereas subplatysmal fat does not.
 - Cervicomenal angle
 - Presence or absence of platysma muscle banding
 - Hypertrophy and/or ptosis of the submandibular glands
 - Hypertrophy of the anterior belly of the digastric muscle
- Nonsurgical interventions include energy-based skin tightening procedures such as Ultherapy (Ultherapy, Mesa, Arizona). Botox (Allergan, Weston, Florida) and Kybella (Allergan, Weston, Florida) can be used for platysmal banding and submental adiposity, respectively.

Surgical Options

Surgical interventions can be grouped into access approaches and adjunctive procedures that can be combined, as indicated based on a patient's preoperative evaluation.

Access approaches

- Liposuction only: generally indicated in younger patients with good skin elasticity and excess preplatysmal fat. Access is via 1 or more stab incisions, as needed.
- Facelift incision: either a short scar technique or postauricular incision can be used depending on the degree of skin laxity. This approach also permits lateral tightening of the SMAS/platysma muscle and correction of the midface.
- Submental incision: a 3-cm to 4-cm submental incision can be used either in isolation or conjunction with the facelift approach. Although the decision whether or not to open the neck may be debated by some investigators [11], this approach permits midline skin subcutaneous undermining for skin redraping

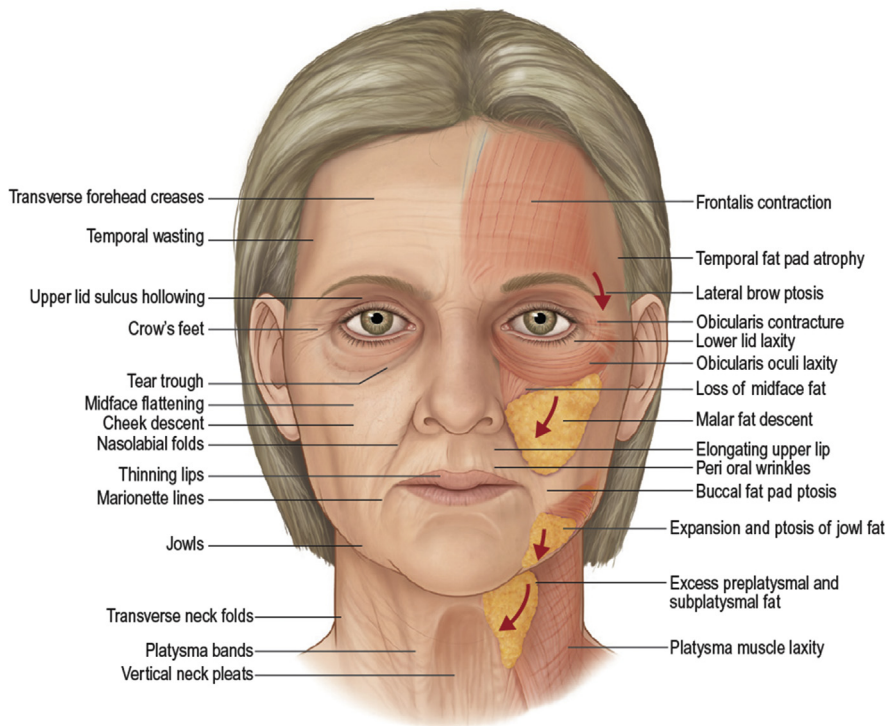


FIG. 4 Appearance of the aged face and neck. Aging changes occur in all tissue layers. Individual treatment plans must be tailored to the specific tissues responsible for aging changes. (From Koh KS, Choi JW, Ishill CH. Asian facial cosmetic surgery. In: Neligan P, editor. Plastic surgery, vol 2. 4th edition. Philadelphia: Elsevier; 2012. p. 185; with permission.)

and tightening, medial platysmaplasty, and direct excision of subplatysmal fat, submandibular glands, and the anterior belly of the digastric muscle [1,5,9,10].

- Direct vertical midline skin excision and Z-plasty: this approach is usually avoided in the author's practice but may be appropriate in the elderly and patients with pronounced midline skin excess.

Adjunctive procedures

- Direct defatting: performed in the subplatysmal plane when indicated. Excess preplatysmal fat can be addressed with liposuction, if present.
- Medial platysmaplasty and/or transverse partial myotomy: helps correct an obtuse cervicomenal angle and medial platysma bands.
- Lateral platysmaplasty and/or transverse partial myotomy: helps further improve the neck profile if there is continued platysma redundancy after medial platysmaplasty.
- Submandibular gland (superficial lobe) resection: indicated in the event of significantly prominent or

ptotic submandibular glands. If not addressed, prominent submandibular glands can become more apparent after neck lift procedures.

- Partial resection of the anterior belly of the digastric muscle: may be indicated in select patients with pronounced muscle hypertrophy.
- Osseous genioplasty or alloplastic chin implant placement: indicated in patients with vertical and/or horizontal microgenia. Helps improve the neck-line appearance on profile view.

Positioning and Surgical Site Preparation

- General endotracheal anesthesia
- Perioperative antibiotics are used, and antiembolism stockings or sequential compression devices are used for the entirety of the case.
- Supine with gentle neck extension
- Foam doughnut to secure head position
- Rolled Xeroform gauze (Covidien, Dublin, Ireland) is placed in each ear canal.
- Entire face is prepped with 5% betadine.

- A sterile towel head drape is placed and secured with clamp.
- A split drape is placed.
- Eyes are irrigated with balanced salt solution and lids are closed with Steri-Strips to prevent corneal irritation.

Procedure Approach

- The surgical field is infiltrated with local anesthetic solution containing 1 mL of 1:1000 epinephrine, 100 mL of 1% lidocaine, and 200 mL of normal saline.
- After waiting for the local anesthetic to take effect, liposuction of the subcutaneous/preplatysmal fat is performed, as indicated. A 2.4-mm Mercedes cannula is used for the neck liposuction and a 1.8-mm Mercedes cannula is used for the jowl area. Additional liposuction is conducted with a spatula tip cannula. Care is taken to not overly skeletonize the neck, because contour irregularities are difficult to treat. Liposuction is generally conservative because the main effect is due to skin undermining and tightening with healing contracture. Patients with minimal skin laxity may be treated by liposuction alone.
- After completion of liposuction, a submental incision is made just above or below the natural submental crease if treatment of the platysmal muscle or subplatysmal fat excision is indicated.
- Wide undermining of the neck skin is performed with the aid of a lighted fiberoptic retractor and the assistant placing countertraction on the skin. Liposuction performed during the prior step greatly assists with definition of this plane.
- Medial platysmal bands are identified. In patients with redundant or hypertrophic anterior platysmal bands, a strip of excess platysmal muscle is excised.
- The subplatysmal plane is entered deep to the medial border of the platysma muscle to directly remove subplatysmal fat, if indicated. This is carried out by directly excising small amounts of fat and melting the remainder with electrocautery.
- Attention is then returned to the platysmal muscle. Various options for the repair of the midline platysmal muscle repair have been described [10,12–15]. The muscle is approximated with interrupted 3-0 Mersiline (Ethicon, San Lorenzo, Puerto Rico) sutures.
- The hyoid fascia can be incorporated into midline platysma repair, as described by Yousif and colleagues [16]. This consists of a 3-way suture passed from 1 platysma, to the hyoid fascia, and to the other platysma, with goal of reducing recurrent platysmal banding and to better contour the platysma to the deep cervical fascia.
- On completion of the midline platysma repair, a medial platysma myotomy is performed at the level of the cricoid cartilage.
- In patients with excess skin or who require midface rejuvenation, the submental subcutaneous direction plane is connected to the preauricular/postauricular access incisions. The neck is completely undermined in the subcutaneous plane under direct vision both sharply and with facelift scissors to permit skin redraping.
- Via the preauricular/postauricular incisions, the lateral border of the platysma is located and evaluated.
 - If the platysma is lax or redundant, it is undermined with sharp and blunt dissection at least 3 cm to 4 cm below the angle of the mandible, back cut, and sutured to the SCM fascia with 3-0 Mersiline suture while avoiding placing excessive tension on the midline repair.
 - In other cases, the platysma is plicated to the SCM at 3 to 4 points, including the lower SMAS for jowl improvement.
- Meticulous hemostasis is attained with bipolar cautery. It is important for the anesthesiologist to raise the blood pressure to the preoperative level while this is performed.
- Jackson-Pratt drains (Cardinal Health, Dublin, Ohio) soaked in betadine are placed and brought out through the wound and sutured.
- Excess skin is elevated, advanced, redraped, and excised to optimize the result and preserve the integrity of the hairline.
- The hair-bearing region is closed with staples and the area between the hair-bearing region and postauricular incision is closed with half-buried absorbable sutures.
- The postauricular crease is closed with 3-0 nylon sutures; the lower preauricular area, if opened for an extended neck lift, is closed with a 5-0 nylon sutures.
- The submental region is the last area inspected for hemostasis after closing both sides of the neck incision. The submental incision is closed with a subcuticular 5-0 prolene suture (Ethicon, San Lorenzo, Puerto Rico).
- Antibiotic ointment is placed on the wounds. A face-lift dressing consisting of gauze and Surginet (Won Industry, Gyeonggi-do, Korea) is placed.

REHABILITATION AND RECOVERY

- Patients are discharged the day of surgery with a head wrap dressing for gentle neck pressure and a Jackson-Pratt drain. A drain is not used if a patient only underwent liposuction.
- Attempts should be made to keep the neck extended in a semisniffing position.

Clinical Results in the Literature

First Author, Year Published	Findings and Results
Aston [3], 1979	Submental incision used to address subcutaneous fat, subplatysmal fat, and submandibular glands, as appropriate. Platysma managed via midline suturing and lateral platysma flap fixation to contour the cervicomenal angle. Partial vertical medial platysma resection is performed prior to midline suturing, if redundancy present. Partial lateral (ie, back cut) vs complete transverse division of the platysma muscle at the level of the cricoid cartilage, depending on the severity of platysmal banding.
de Castro [17], 1980	Described 3 subtypes of midline platysma muscle relationships • Type 1: medial platysma fibers interlace for 1–2 cm below the gnathion • Type 2: medial platysma fibers interlace from the gnathion down to the level of the thyroid cartilage • Type 3: the paired platysma muscles do not interlace
Martin [18], 2008	Facelift incision and submental incision placed 1 cm posterior to the submental crease. Neck completely elevated in subcutaneous plane for skin redraping. Subplatysmal fat directly excised, inferior lobe of submandibular gland resected, and shave excision of anterior belly of digastric performed, if necessary. Lateral subplatysmal dissection performed to elevate muscle from the sternocleidomastoid and inferior lobe of the parotid. Medial platysma reapproximated with buried interrupted suture to level of hyoid bone. SMAS/platysma flap elevated in posterosuperior vector and anchored to the deep temporal fascia superiorly. No anchoring of SMAS/platysma to mastoid or sternocleidomastoid fascia.
Mustoe et al [11], 2010	Case series, 742 deep plane facelift patients. Neck approached laterally in subplatysmal plane with release of cervical retaining ligaments, including platysmal attachments to anterior border of sternocleidomastoid, posteroinferior mandibular border, and inferomedial border of parotid and submandibular gland. Submental incision avoided—performed in only 1.8% of patients. Subcutaneous undermining with liposuction cannulas (no suction) for skin redraping. Hematoma incidence: 0.5% Surgical site infection incidence: 1%
Pelle-Ceravolo et al [19], 2016	Case series, 150 patients, 96 presented for 1-y follow-up Neck approached via submental and facelift incision. Complete transverse division of platysma at level of cricoid cartilage medially to 4–5 cm inferior to mandibular border laterally. Muscle sutured in midline and suspended laterally. Subcutaneous lipectomy (34.6%), subplatysmal lipectomy (30%), submandibular gland reduction (9.3%), and digastric shaving (1.3%) were performed, as appropriate. Hematoma rate: 2.6% 76.1% of patients reported results as “good” to “beyond expectations” at 1 y postoperative. At 1 y postoperative, 35.4% of patients had recurrent platysmal bands and 43.7% had some recurrent skin laxity.
Pelle-Cervello et al [20], 2017	Case series, 100 patients, 73 presented for 1-y follow-up. Neck approached laterally via facelift incision without a submental incision. A superiorly based medial platysma flap developed and transected at level of cricoid cartilage. Medial platysma flap secured to mastoid fascia. Hematoma rate: 2.1% 28% underwent subcutaneous liposuction, 24% underwent submandibular gland resection. 100% of patients reported results as good to “beyond expectations” at 1 y postoperative. At 1-y postoperative, 11% with recurrent platysmal bands and 26% with some recurrent skin laxity.

- Patients are seen in clinic the day after surgery and drains are removed if output is less than 30 mL since surgery. Antibiotic ointment is applied over the suture lines.
- The patient is continued on preoperative antihypertensive medication regimen, if applicable.
- Strenuous activity or bending at the waist is avoided for 2 weeks after surgery.

POTENTIAL COMPLICATIONS/RISKS/BENEFITS/LIMITS

- Isolated neck procedures address the area contained between the clavicles and inferior mandibular border. A properly selected and executed surgical intervention can result in significant aesthetic improvement.
- Isolated neck procedures do not address aging changes in the lower or middle facial thirds.
- Patients must be educated about the limits of isolated neck rejuvenation to address unrealistic expectations and avoid dissatisfaction.
- Complications vary depending on the extent of the procedure that is performed and include
 - Seroma and hematoma, with the latter the most feared complication, occurring in approximately 1% of cases [11,21]
 - MMN palsy
 - Sialocele
 - Skin necrosis

MANAGEMENT

- Hematoma: prompt recognition is key, because large hematomas can result in airway compromise and skin flap necrosis. Although smaller hematomas may not be life-threatening, they must be evacuated because failure to treat results in scarring and contour irregularities that are difficult to treat. Large hematomas require return to the operating room whereas smaller ones can be aspirated with a large gauge needle.
- Seroma: these should be serially drained by aspiration until resolved.
- MMN palsy: conservative management is used. Postoperative palsy is due to neuropraxia in a majority of cases and is expected to resolve within 3 months after surgery. Contralateral depressor angularis oris neurotoxin injections can be used as a temporizing measure to improve smile symmetry while the neuropraxia resolves.
- Sialocele: serial aspiration, pressure dressings, anticholinergics, and Botox injections can be used.
- Skin necrosis: as with hematoma, prompt recognition is key. Nitroglycerin ointment is applied in the operating room over areas of marginal vascularity. If applicable, exacerbating factors, such as hematoma, seroma, and excessive skin tension, must be addressed.

SUMMARY/DISCUSSION

Submentoplasty

Neck aging	• Occurs in conjunction and often more rapidly or can be more apparent than facial aging. • It is a result of changes in the skin, platysma, and fat of the neck. Other structures, such as the digastric muscle and submandibular glands, can also contribute to neck aging. • Nonsurgical treatments offer improvement when directed at the appropriate layer of tissue. • The most comprehensive treatment of the aging neck is a surgical neck lift.
Fat removal	• Isolated liposuction and submentalplasty can produce significant results in patients with preplatysmal adiposity and good skin elasticity. • Preplatysmal liposuction should be conservative to prevent contour irregularities. • Preplatysmal liposuction and/or subplatysmal fat excision is a critical component of all neck lift procedures, as indicated based on the location of excess fat.
Medial platysmaplasty	• After any platysma redundancy is removed, it is repaired in the midline, which, when complete, resembles the Eiffel Tower. • The platysma is back cut at the level of the cricoid cartilage. • The hyoid fascia can be incorporated as a potential means of potentially reducing recurrent platysma banding [16].
Lateral platysmaplasty	• If there is insufficient improvement of the cervicomental angle with medial platysmaplasty, lateral platysmaplasty is used to further improve the neck profile. • The lateral platysma is undermined at least 3–4 cm below the angle of the mandible, back cut, and sutured to the SCM fascia. • In other cases, the platysma is plicated to the SCM at 3 points, including the lower SMAS for jowl improvement.

Submandibular gland partial excision

- Treatment of submandibular gland hypertrophy or ptosis is arguably the most controversial aspect of neck rejuvenation due to potential postoperative complications, including bleeding, facial nerve palsy, and sialoceles.
- Several investigators have advocated suture suspension techniques [22–28], whereas others have questioned the longevity of these procedures [29].
- When indicated, submandibular gland superficial lobe resection can significantly improve submandibular triangle soft tissue bulging [8,30,31].
- The submandibular gland capsule is entered at its caudal edge, below the crossing MMN [8]. The superficial lobe is carefully dissected to control vessels before resection.

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Treatment of Striae

Are There Effective Treatments?

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KEYWORDS

- Striae • Striae rubra • Striae alba • Striae distensae • Microneedling • Pulsed dye laser
- Nonablative fractionated lasers • Ablative fractionated lasers

KEY POINTS

- Striae are a common type of atrophic scar that has proven difficult to treat.
- Topical treatments have been studied but have the lowest efficacy for change.
- Light-based and laser-based treatments have a good treatment efficacy for striae rubrae, but mostly improve texture in striae alba.
- Radiofrequency treatments for striae also are helpful, with texture being the most noted improvement.
- A complete resolution of striae is rare. Combination treatments, laser-assisted drug delivery, and other modalities are likely the future treatment of striae.



Video content accompanies this article at www.advancesincosmeticsurgery.com.

INTRODUCTION

Striae distensae, or stretch marks, are common atrophic scars that can be symptomatic and cosmetically concerning [1]. The development of striae has been associated with pregnancy, growth spurts, obesity, rapid weight gain or loss, rapid muscle growth, breast augmentation, diabetes mellitus, long-term systemic or topical steroid use, prolonged adrenocorticotrophic hormone therapy, Marfan syndrome, and Cushing syndrome [2,3]. Striae rubra are the early form of striae that are characteristically pink, and striae alba are the end stage of striae with atrophic white scars [4,5].

Surgical Technique

The surgical technique varies depending on the device used, which is explained in greater detail with each device.

Preoperative Planning

Most devices used for the treatment of striae have minimal to no down time and require nominal preoperative planning. Avoidance of sun exposure is key before treatment, and postoperatively varies per procedure performed. Avoidance of treatment in pregnancy also is recommended.

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Preparation and Patient Positioning

Before the procedure, it is recommended to gently cleanse the treatment area and dry the skin. The patient should be positioned in a way that allows for the physician to have proper access to the treatment zone while allowing patient comfort. Topical anesthesia with varying percentages of lidocaine can be applied 30 to 60 minutes before the procedure to minimize pain, and is classically used for all modalities discussed in this article other than when vascular lasers are used for the treatment of striae rubra. In addition, cool air devices may be added during the procedure to minimize treatment pain.

Immediate Postprocedural Care

If gels or fluids are applied for the procedure, these are removed with saline-soaked gauze. A bland dimethicone or petrolatum-based ointment is used after ablative procedures and is applied immediately after postprocedure for several times a day for a minimum of 1 week after the procedure. If a nonablative laser or device is used, a bland moisturizer is typically applied immediately postprocedure, and used several times daily for several days after the procedure. Sun avoidance is recommended, along with a daily broad-spectrum mineral-based sunscreen. Daily cleansing of the treatment area with soap and water also is recommended.

Rehabilitation and Recovery

The recovery time for each device is different and can range from 1 to 4 weeks. Vascular lasers may leave ecchymoses that can last 1 to 2 weeks, whereas nonablative and ablative devices may leave erythema that can last 1 to 4 weeks depending on the body area treated and the energy and density used. Ablative devices would require additional recovery time, whereas nonablative devices would require less.

Potential Complications, Risks, Benefits, and Limits

Complications with the nonablative, ablative, and microneedle radiofrequency (RF) devices can include infection, hyperpigmentation, hypopigmentation, erythema, edema, burns, and crusting. The risk of these complications varies with each device and increases with more aggressive settings. The more aggressive the settings or the darker the skin type, prolonged postoperative erythema can increase the risk of post-inflammatory hyperpigmentation. If too much ecchymoses is induced with a vascular laser, hemosiderin deposition and staining may occur. Lasers have a

limitation in their settings based on skin type, whereas RF devices do not. The benefits most often outweigh the risks providing patients expectations of improvement of their striae.

Management

Multiple treatments are often needed with any of the modalities. Treatment intervals vary on the device used and are discussed in further detail later in this article. A 3-month to 6-month follow-up after the last treatment is ideal to assess an improved treatment outcome, as most modalities rely on neocollagenesis. Texture is the most common improvement noted. A complete resolution of the striae is rare.

Please see Tables 1 and 2 for summaries of the clinical research in the treatment of striae.

TREATMENT OF STRIAE

Multiple treatment modalities for striae have been published with mixed outcomes. The best results have been noted with striae rubra [4]. Both the increased vascularity and the atrophic aspect of the scar need to be addressed to obtain a cosmetically pleasing result (Fig. 1) [6].

TOPICAL TREATMENT OF STRIAE

Topical treatments have been studied to prevent striae distensae with minimal success. Osman and colleagues [7] (n = 210) examined the prevention of striae alba and found no improvement with the use of topical cocoa butter. However, Timur Taşhan and Kafkasli [8] (n = 47) found a 20% decrease in the risk of developing striae with the combination of massage and topical bitter almond oil.

Minor improvements were found with topical treatments for striae rubra. Kang [9] (n = 22) found an 80% improvement of striae rubra with 0.1% tretinoin cream daily for 6 months. Draelos and colleagues [10] (n = 10) found an overall improvement of the appearance, texture, color, and softness of striae rubrae with daily 3-month applications of onion extract cream with *Centella asiatica* and hyaluronic acid (Mederma stretch mark therapy; Merz, Raleigh, NC).

Mixed results have been seen with the topical treatment of striae rubra and alba. Rangel and colleagues [11] (n = 20) found a 20% decrease in striae length after a daily 3-month application of 0.1% tretinoin cream. Elson [12] (n = 20) found 75% of subjects had significant improvement of their striae rubra and alba with a daily 3-month application of 0.1%

TABLE 1
Laser and Light Treatment of Striae Distensae

Study	Laser/Light Treatment	Wave-Length, nm	Chromophore Target	Ablative (A) vs Nonablative (NA)	Fractionated (F) vs Nonfractionated (NF)	Treatment	Result
Goldberg et al [22], 2003, n = 15	Excimer	308	Protein	NA	NF	8.4 treatments of striae alba	Increased melanin, melanocytes noted
Goldberg et al [23], 2005, n = 5	UVB Laser	311–313	Protein	NA	NF	10 treatments of UVB on striae alba	Increased melanin and melanocytes noted
Mendoza-Garcia et al [21], 2015, n = 18	Red Light PDT	635	Blood	NA	NF	5-ALA or MAL PDT ex vivo skin	Increased MMP3 and ELN noted
McDaniel et al [24], 1996, n = 39	PDL	585	Blood	NA	NF	1 treatment of striae with 4 different settings	Lower energy densities improved appearance of striae; increased elastin noted POW8
Nehal et al [25], 1999, n = 5	PDL	585	Blood	NA	NF	Treated striae alba every 2 mo for 2 y	No improvement noted with striae alba
Jimenez et al [26], 2003, n = 20	PDL	585	Blood	NA	NF	2 treatments 6 wk apart with a 12 wk f/u	Striae rubra improved but striae alba did not
Hernandez-Perez et al [19], 2002, n = 15	IPL (nonlaser)	515–1200 (695)	Blood	NA	NF	5 IPL sessions at 2-wk intervals	General appearance, number, and size improved

(continued on next page)

TABLE 1
(continued)

Study	Laser/Light Treatment	Wave-Length, nm	Chromophore Target	Ablative (A) vs Nonablative (NA)	Fractionated (F) vs Nonfractionated (NF)	Treatment	Result
Goldman et al [27], 2008, n = 22	Nd:YAG Long pulsed	1064	Water	NA	NF	Striae rubra were treated an average of 3.45 times every 3–6 wk	55% subject-rated and 40% physician-rated improvement
Gungor et al [28], 2014, n = 20	Nd:YAG Long pulsed vs VSP Erbium	1064 2940	Water Water	NA A	NF NF	Split abdomen study with 3 monthly treatments	Striae alba had no change; striae rubra had moderate change but not significant
Young-Kwang et al [46], 2006, n = 11	Diode	1450	Water	NA	NF	3 treatments at 6-wk intervals	No noticeable improvement; PIH in 64% of patients
de Angelis et al [31], 2011, n = 51	Erbium: glass	1540	Water	NA	F	2–3 passes completed with 2–4 treatments every 4–6 wk	≥50% improvement of striae rubra and alba 6 mo posttreatment; PIH, erythema, and edema resolved
Malekzad et al [32], 2014, n = 10	Erbium: glass	1540	Water	NA	F	4 treatments at 4-wk intervals	1%–24% improvement noted 3 mo posttreatment
Bak et al [33], 2009, n = 22	Fraxel SR	1550	Water	NA	F	2 treatments 4 wk apart	27% had excellent improvement and 63% had varied improvement; striae alba responded best
Stotland et al [34], 2008, n = 20	Fraxel SR	1550	Water	NA	F	6 treatments at 2–3-wk intervals for striae rubra and alba	26%–50% overall improvement noted in 63% and texture improvement in 50%

Tretti Clementori & Lavagno [35], 2015, n = 12	Erbium: glass (ResurFX)	1565	Water	NA	F	3 treatments completed	51%–75% improvement noted in all subjects. Most had >50% volume of depression improvement
Zaleski- Larsen et al [36], in press, n = 20	Picosecond Nd:YAG vs Erbium:glass (ResurFX)	1064/532 1565	Water Water	NA NA	F F	Split abdomen comparative study with 3 monthly treatments	• 31% texture improvement for both lasers • 30%–35% improvement in atrophy • 45%–48% overall improvement
Gauglitz et al [37], 2014, n = 2	Erbium:YAG and PDL	2940 585	Water Blood	A NA	F NF	Combination single treatment of axillary striae	Moderate improvement noted
Nouri et al [30], 1999, n = 4	CO ₂ short pulsed PDL	10,600 585	Water Blood	A NA	NF NF	Skin types IV–VI were treated once with the CO ₂ and the PDL	No improvement was noted in the striae; persistent erythema and PIH were noted with the higher skin types
Lee et al [38], 2010, n = 27	CO ₂	10,600	Water	A	F	Single treatment of striae with Deep FX mode	Improvement 0%–25% in 7.4%, 26%–50% in 33%, 51%–75% in 51.9%, >75% in 7.4%
Naeini et al [39], 2014, n = 3	CO ₂ PDL	10,600 585	Water Blood	A NA	F NF	Combination single treatment	Combination treatment was better than either alone

Abbreviations: 5-ALA, 5-aminolevulinic acid; ELN, tropoelastin; f/u, follow-up; IPL, intense pulsed light; MAL, methylaminolevulinate; MMP3, metalloproteinase 3; Nd, neodymium-doped; PDL, pulse dye laser; PIH, postinflammatory hyperpigmentation; POW8, post-operative week 8; YAG, yttrium aluminum garnet.

TABLE 2
Radiofrequency Treatment of Striae

Study	Radiofrequency Device	Polarity	Application	Ablative (A) vs Nonablative (NA)	Fractionated (F) vs Nonfractionated (NF)	Treatment	Result
Manuskiatti et al [41], 2009, n = 17	TriPollar (Apollo, Pollogen Ltd., Tel Aviv, Israel)	Tripolar	Topical noninvasive	NA	NF	6 weekly treatments	6 wk after treatment 12% of subjects were slightly satisfied, 23% were satisfied, and 65% were very satisfied
Dover et al [40], 2014, n = 16	Venus Freeze	Bipolar	Topical noninvasive	NA	NF	6 monthly treatments	87.5% subjects noticed a visible change; reduction in length and width noted
Ryu et al [44], 2013, n = 30	Microneedle RF (Secret; ilooda) • CO ₂ laser	Unipolar	Fractionated grid needle pattern	A A	F F	Fractional CO ₂ laser only, RF only, and combination with single treatment session	Improvement 2.2/4 with the CO ₂ , 1.8/4 with RF, and 3.4/4 with the combination
Suh et al [43], 2007, n = 37	• Thermage • PDL laser	Unipolar	Topical noninvasive	NA	NF	Thermage and PDL laser combined with 2 treatments 1 mo apart	89.2% had good overall improvement and 59.4% had good elasticity improvement; increased collagen seen with all patients
Issa et al [45], 2013, n = 8	• Fractional ablative RF (Pixel roller; in motion tip) • Topical Retinoic acid 0.05% cream • Acoustic Pressure Ultrasound	Bipolar	Fractionated	A	F	Comparison of the combination of Fractional RF, topical retinoic acid and ultrasound with Fractional RF alone	• No significant improvement with RF alone • Improvement from severe to moderate in 3/8, moderate to mild in 2/8, and 2/8 severe to mild with the combination treatment

Abbreviations: ELN, tropoelastin; PDL, pulse dye laser; RF, radiofrequency.



FIG. 1 A 38-year-old woman who completed a single treatment with the 1565-nm Erbium:glass laser (ResurFX; Lumenis, Yokneam, Israel) on the right and the picosecond fractional 1064/532 nm Nd:YAG laser (Picoway; Syneron Candela, Irvine, CA) on the left. The photo on the right reveals a visual improvement of her striae 3 months postprocedure.

tretinoin. Pribanich and colleagues [13] ($n = 11$) found no improvement of striae compared with placebo with the use of topical 0.025% tretinoin cream daily for 8 months. Additional larger studies are needed to fully evaluate the efficacy of these treatments.

DERMABRASION

Hexsel and colleagues [14] ($n = 32$) compared topical 0.05% tretinoin and a superficial localized dermabrasion (LB100; Beltec, Araraquara, Brazil) in the treatment of striae rubra and found a similar treatment efficacy. However, dermabrasion was found to have better patient adherence and fewer side effects. Ibrahim and colleagues [15,16] ($n = 68$) found intradermal platelet-rich plasma treated in 6 sessions 2 weeks apart to be more effective than microdermabrasion alone with a more rapid improvement when used in combination with microdermabrasion.

NEEDLING THERAPY

Through the induction of neocollagenesis, needling therapy can improve the appearance of scars [17]. Park and colleagues [18] ($n = 16$, mean age 31.7 years) found 43.8% (7/16) of the subjects had an excellent

improvement and 56.2% (9/16) of patients had minimal to moderate improvement of striae rubra and alba on the thighs, buttocks, or abdomen 3 months after 3 monthly microneedle (DTS roller; DTS-MG, Inc., Seoul, Korea) treatments. Topical anesthetic cream (eutectic mixture of local anesthetics; AstraZeneca, Wilmington, DE) was applied for 1 hour before the procedure. The treatment was performed 4 times in 4 directions, ensuring a density of 600 to 750 dots/cm². A moisturizer (Cicaplast; La Riche-Posay, Paris, France) was applied 3 times daily for 2 weeks after the treatment. Baseline and 3-month posttreatment biopsies were completed and showed a thickened epidermis and increases in dermal collagen and elastic fibers post-treatment. Side effects were considered to be tolerable, including erythema, mild pain, and spotty bleeding [18].

LIGHT-BASED TREATMENT OF STRIAE

Hernandez-Perez and colleagues [19] ($n = 15$) evaluated skin types III–IV with 5 intense pulsed light (IPL) 645-nm cutoff filter, 90 J/cm² with a double-pulse length of 2.7 to 4.0 ms with a 20-ms delay (VascuLight Plus; Lumenis; Yokneam, Israel), sessions at 2-week intervals with an overall improvement in the general

appearance, number, and size of the striae 2 weeks after the last treatment. Shokeir and colleagues [20] ($n = 20$) compared the 656-nm IPL cutoff filter (Medical Bio Care, Gothenburg, Sweden), spot size 10×20 mm, pulse duration of 50 to 70 ms, and 17.5 J/cm^2 with the 585-nm pulse dye laser (PDL) laser (Cynosure, Westford, MA), 10-mm spot size, 0.5-ms pulse duration, 2.5 J/cm^2 , in the treatment of striae rubra and alba in skin types III–IV. Five sessions at 4-week intervals were completed and a 4-mm punch biopsy was taken before treatment and 1 month after treatment. Striae rubra responded better than striae alba, and the PDL induced more collagen stimulation than the IPL, as noted with Masson trichrome staining; however, both were considered effective treatments (see Table 1).

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) also has been used to treat striae. Mendoza-Garcia and colleagues [21] ($n = 18$) applied 5-aminolevulinic acid (ALA) or methylaminolevulinate (MAL) in combination with the red light at 635 nm, 40 J/cm^2 to treat striae alba in this *ex vivo* study. Histologic examination was completed with hematoxylin-eosin, Herovici, and Weigert staining; apoptosis; proliferation; metalloproteinase 3 (MMP 3); and tropoelastin expression quantifications. Apoptosis increased, proliferation decreased, and proliferating cell nuclear antigen gene expression decreased after PDT treatment. Collagen 1 and Collagen III gene expression levels decreased, whereas MMP3 and tropoelastin significantly increased after PDT compared with normal skin. Both the ALA-treated and MAL-treated skin had similar results.

NONABLATIVE LASER TREATMENT OF STRIAE

Excimer

Goldberg and colleagues [22] ($n = 75$) noted an 80% improvement in repigmentation of striae alba with the 308-nm Excimer laser (XeCl Excimer; Xtrac PhotoMedex, Radnor, PA) with an average of 8.4 treatments. A train of 30-ns pulses was used at a repetition rate of up to 250 Hz delivered through a fused silica fiber to a handpiece over a 1.8×1.8 -cm exposure field with a minimal erythema dose determined for all patients before treatment. The first treatment dose was started at the minimal erythema dose with an increase of 10% in dose with each subsequent treatment until a $>75\%$ improvement was noted or a

maximum of 15 treatments. Additionally, Goldberg and colleagues [23] ($n = 10$) found increased melanin content, hypertrophy of melanocytes, and an increase in melanocyte number in striae alba for both the Excimer laser (XeCl Excimer; Xtrac PhotoMedex) and the UVB 311-nm to 313-nm laser (ReLume; Lumenis, Santa Clara, CA).

Pulse Dye Laser

McDaniel and colleagues [24] ($n = 39$) used the 585-nm PDL (Cynosure, Bedford, MA) to treat striae rubra at different settings. The striae were treated with a single 450- μs pulse with either a 7-mm or 10-mm spot size and a fluence ranging from 2.5 to 4.0 J/cm^2 with 1 total treatment and follow-up at 8 weeks after the procedure. Energy levels above 4 J/cm^2 did not produce any improvement in treatment outcome and improvements were gradual over several months to a year. Striae treated with a 10-mm spot size and 3 J/cm^2 had the greatest clinical improvement of erythema, although all treatment settings revealed some degree of improvement. Nehal and colleagues [25] ($n = 5$) did not find any improvement of striae alba with the 585-nm PDL with a 450-ms pulse, 10-mm spot size, and 4.25 J/cm^2 fluence (SPTL-1b; Candela Corp, Wayland, MA). Jimenez and colleagues [26] ($n = 20$) found a moderate beneficial effect of the erythema of striae rubra but no change with striae alba with the 585-nm PDL (Cynosure VLS, Chelmsford, MA). Overall, a larger spot size of 10 mm, 450- μs pulse, and energy levels $\leq 4 \text{ J/cm}^2$ are considered ideal for the treatment of striae rubra.

Neodymium-Doped Yttrium Aluminum Garnet

Goldman and colleagues [27] ($n = 22$) found that 55% of subjects rated themselves as excellent using subject global aesthetic improvement scores, and 40% of physicians rated improvement excellent of striae rubra with the 1064-nm-long pulsed neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (Smartepil; DERA, Firenze, Italy). Cool air or ice packs were applied pre-treatment and a thin layer of cold water-based gel was applied to the treatment areas. A spot size of 2.5 mm, 80 to 100 J/cm, and a delay of 15 to 20 ms with a frequency of 2.0 Hz was used with an average of 3.45 treatments at 3-week to 6-week intervals. Gungor and colleagues [28] ($n = 20$) compared the nonablative 1064-nm-long pulsed Nd:YAG with the nonablative 2940-nm Variable Square Pulse (VSP) Erbium laser (Fotona, Ljubljana, Slovenia) with 3 monthly treatments and found no clinical improvement in striae alba in skin types II to V. However, striae

rubra had a moderate improvement of erythema. Before treatment, a eutectic mixture of local anesthetics (EMLA) was applied occlusively for 45 minutes and cleansed with distilled water. Cool air was used during the procedure to minimize discomfort. VSP Erbium treatment settings included with one pass in the smooth mode (250 ms) at 3.2 J, 7-mm spot size, and 50% overlap followed by 2 passes in the short pulse mode (0.3 ms) at 1 J, 7-mm spot size with a 50% overlap. The LP Nd:YAG laser treatment settings included 2 passes with the 50-ms pulse duration at 50 J/cm² with a 6-mm spot size and 50% overlap. A fragrance-free moisturizer was applied 3 times daily for a week after the procedure [28].

Diode

Tay and colleagues [29] (n = 11) found no improvement of striae rubra and alba with the 1450-nm diode laser (Smoothbeam; Candela Corp; Wayland, MA) in skin types IV to VI, 2 months after the last treatment. Topical anesthetic cream (EMLA; AstraZeneca, Cambridge, UK) was applied for 1 hour before the laser procedure. A single nonoverlapping pass with a spot size of 6 mm and either 4, 8, or 12 J/cm² was used. Three treatments were completed at 6-week intervals. Postinflammatory hyperpigmentation was noted in 65% of the subjects.

ABLATIVE LASER TREATMENT OF STRIAE

Nouri and colleagues [30] (n = 4) found no improvement of striae alba in skin types IV to VI with a single treatment with the short-pulsed CO₂ laser (Coherent, Santa Clara, CA) or the PDL (Cynosure, Bedford, MA). For the Coherent short-pulsed CO₂ laser treatment, the skin was first anesthetized with 1% lidocaine. A 3-mm spot size at 400 mJ on the first pass followed by a second pass of 350 mJ after a saline wash to remove any eschar was then completed. The PDL laser treatment had no prior anesthesia and used a 10-mm spot size, 3 J/cm² with a final follow-up at 4 months postprocedure. Postinflammatory pigmentation continuation was noted with the darker skin types in this study.

FRACTIONAL NONABLATIVE TREATMENT OF STRIAE

de Angelis and colleagues [31] (n = 51) found a 50% to 75% improvement of striae rubra and alba 3 months after 2 to 4 treatments with the Erbium:glass 1540-nm fractional nonablative laser (Lux

1540; Palomar Medical Technologies, Inc., Burlington, MA). Skin was pretreated with a compound of 1% hydrocortisone, 4% hydroquinone cream, and 3% vitamin C to the patients' striae for 30 days before treatment. Immediately pretreatment, ice was given to decrease discomfort. A range of energy settings was used between 35 and 55 mJ/μbeam with the 10-mm tip and 12 to 14 mJ/μbeam with the 15-mm tip. After treatment, subjects applied moisturizing cream multiple times per day to maintain hydration and reduce erythema for up to 6 months. Malekzad and colleagues [32] (n = 10) reported a noticeable improvement compared with baseline 3 months after the fourth monthly treatment with the 1540-nm fractional nonablative laser (Star Lux 500; Palomar Medical Technologies, Inc.).

Bak and colleagues [33] (n = 22) found that 27% of subjects had good to excellent improvement and 63% had some improvement of striae rubra and alba in Fitzpatrick skin type IV at 1 month after 2 treatments 4 weeks apart with the 1550-nm Fraxel SR fractional nonablative laser (Fraxel; Solta Medical Inc., Hayward, CA). Topical lidocaine gel 30% was applied for 1 hour before the procedure. Each treatment used a 30-mJ pulse energy, density level 6 (17% coverage), and 8 passes. Skin biopsy samples were taken from the most atrophic site before treatment and 1 month after the last treatment. Hematoxylin-eosin, Masson trichrome, and Elastic van Gieson stains were completed. Increased dermal thickness was noted after treatment; however, there was similar elastin staining as noted in the elastic von Gieson staining before and after treatment. Additional improvements may have been noted with a longer follow-up.

Stotland and colleagues [34] (n = 20) found striae improvement in 26% to 50% of patients 3 months after the sixth biweekly treatment with the 1550-nm Erbium-doped fiber fractional nonablative laser (Fraxel Re:Store; Solta Medical Inc.). The greatest improvement was a 26% to 50% improvement of texture. The treatment protocol consisted of a pretreatment gentle cleanser, a wipe of 70% alcohol, and a topical lidocaine 30% cream applied for 1 hour before the treatment. A blue-tinted tracking gel (opti-Guide Blue; Reliant Technologies, San Diego, CA) was applied to the treatment area along with forced cool air. Laser settings included a 12-J/cm² to 18-J/cm² fluence with 125-MTZs/cm² to 250-MTZs/cm² density and 8 to 12 passes for a total energy delivery of 1.4 to 3.5 kJ per session. Posttreatment instructions included cleansing the skin daily with a mild soap and to avoid sun exposure.

Tretti Clementoni and Lavagno [35] ($n = 12$) reported a 51% to 75% overall striae improvement, a 91.7% volume of depression improvement, and an 83.3% color improvement after 3 treatments with the 1565-nm Erbium:glass (ResurFX; Lumenis, Yokneam, Israel) laser. Similarly, Zaleski-Larsen and colleagues [36] ($n = 20$) compared the 1565-nm Erbium:glass laser (ResurFX; Lumenis, Yokneam, Israel) and the picosecond fractional 1064/532-nm Nd:YAG laser (Picoway; Syneron Candela, Irvine, CA) in a split abdomen study. A 31% improvement in texture was noted for both lasers. The 1565-nm Erbium:glass laser had a 30% improvement in atrophy and a 48% overall improvement, whereas the picosecond 1064/532-nm Nd:YAG treatment had a 35% improvement in atrophy and a 48% overall improvement. Pretreatment included cleansing the area with an alcohol swab. The picosecond 1064-nm laser settings included the fractionated handpiece with a 6-mm spot size, 1.3-mJ/ μ beam, 10 Hz, with 4 passes. This was immediately followed by the picosecond 532-nm laser using the fractionated (Resolve; Syneron Candela) handpiece with a 6-mm spot size, 0.4 mJ/ μ beam, and 2 passes. The 1565-nm laser used a 12-mm square spot size, a spot density of 400 mb/cm², 0.5 to 2.0 Hz, 40 J, and 1 pass with the sapphire tip, as seen in Fig. 1. The endpoint for all lasers was localized erythema. A total of 3 treatments were completed with a 3-week interval between treatments. The picoway laser treatment time was significantly faster in comparison with the fractionated 1565-nm laser, with approximately one-fourth the treatment time. A bland dimethicone-based ointment (Vaniply; Pharmaceutical Specialties, Inc., Rochester, MN) was applied to treated areas postprocedure. See Video 1 for a demonstration of this technique [36].

FRACTIONAL ABLATIVE TREATMENT OF STRIAE

Erbium:YAG Laser

Gauglitz and colleagues [37] ($n = 2$) found a moderate improvement of striae with a single combination treatment with the PDL laser (Syneron Candela) followed by the 2940-nm fractional ablative Erbium:YAG laser (Sciton Inc, Palo Alto, CA) on the same day.

CO₂ Laser

Lee and colleagues [38] ($n = 27$) found 7.4% of subjects had a 4 of 4 improvement, 51.9% had a 3 of 4 improvement, 33.3% had a 2 of 4 improvement, and

7.4% had a 1 of 4 improvement 3 months after a single treatment with the 10,600-nm CO₂ laser (DeepFX CO₂ laser; Lumenis, Santa Clara, CA). The Deep FX mode was used with a pulse energy of 10 mJ (300- μ depth), spot size of 1 to 10 mm, 300 Hz, and a density of 2 (10% coverage) with a single pass. An epidermal cooling device (Zimmer Medizin Systems, Irvine, CA) was used during the procedure to reduce pain. After the procedure, a bland moisturizer (Cicaplast; La Roche-Posay, Paris, France) was applied several times daily for several days after the treatment. A broad-spectrum sunscreen (Anethelios XL; La Roche-Posay) was used after therapy until crusting subsided and sun avoidance was instructed. Naeini and colleagues [39] ($n = 88$) reported a combination treatment of the CO₂ laser and PDL had a better improvement than either treatment alone in the treatment of striae alba.

RADIOFREQUENCY DEVICES

An overview of RF devices used in the treatment of striae is shown in Table 2. Dover and colleagues [40] ($n = 16$) reported an 87.5% subject-rated improvement and 14 of 16 subjects with a striae length and width improvement of an average of 1.031 cm after 6 monthly treatments with the bipolar RF device (Venus Freeze; Venus Concept; Toronto, Ontario, Canada). Before treatment, the skin was cleansed with a gentle cleanser and dried. Treatment parameters were determined by the physician depending on skin type and the treatment area. Length of treatment was approximately 10 minutes for a 4 $\times$ 5-inch area with an energy output of 60% to 80% as the therapeutic goal that was to be reached within the first minute of treatment. Manuskiatti and colleagues [41] ($n = 17$) found 65% of subjects were very satisfied with their striae 6 weeks after 6 weekly treatments with the TriPollar RF (TriPollar; Pollogen Ltd, Tel Aviv, Israel). Preoperatively, no local anesthesia was used. A thin layer of glycerin oil was placed on the treatment area and the applicator was moved with slight pressure in a continuous sweeping motion over the skin. An average of 47 W (range 40–50 W) of RF energy was administered with a frequency range of 1 MHz to the treatment area. The energy levels were adjusted according to the subject's feelings and skin reactions. The treatment sites were treated until the skin temperature increased to 40° to 42°C for approximately 2 minutes on each treatment site. The skin temperature was monitored with a handheld infrared thermometer (Mini-Temp MT4; Raytek Corp, Santa Cruz, CA). No postoperative care was required [41, 42].

Combination Treatments

Combination treatments appear to have the largest treatment success for striae. Suh and colleagues [43] ($n = 37$) reported 89.2% of subjects had a “good to very good” overall improvement and 59.4% had good to very good elasticity improvement with the combination of the PDL laser (V-star; Cynosure, Bedford, MA) and the monopolar RF (Thermage, ThermoCool TC; Thermage Inc, Hayward, CA). Topical anesthetic cream was applied before the Thermage procedure under occlusion for 60 minutes. Thermage was used at fluences ranging from 53 to 97 J/cm² (dial setting level of 10.5–13.5) with 2 to 3 nonoverlapping passes using the standard tip through conductive fluid. Immediately after treatment the conductive fluid was removed with saline-soaked gauze, and cool compresses were applied for 15 minutes. The PDL treatment used a fluence of 3 J/cm², a 10-mm spot size, and a 0.5-ms pulse duration. A 2-mm punch biopsy was completed before treatment and 2 weeks after treatment. Hematoxylin-eosin and Victoria blue stains were used and showed increased collagen with scant elastic fiber increases and no change in epidermal thickness. Ryu and colleagues [44] ($n = 30$) found the combination of the noninsulated fractionated microneedle RF device (Secret; ilooda, Suwon, South Korea) and the fractional 10,600-nm CO₂ laser (CICU2; ilooda) provided the largest improvement 1 month after the last treatment of a 3.4 of 4 compared with a 2.2 of 4 improvement with the fractional CO₂ laser alone and a 1.8 of 4 improvement with the microneedle RF device alone. A total of 3 treatment sessions 1 month apart were completed. A topical eutectic mixture of 2.5% prilocaine (EMLA; Astra-Zeneca, Sodertalje, Sweden) was applied under occlusion 30 minutes before the procedure. The fractional CO₂ laser settings included 700 to 1000 mJ, 0.7-mm density with 1 pass. The fractional RF treatment settings included a 1.5 to 3-mm microneedle penetration depth, 4 to 7 intensity, and 70 to 130-ms RF conduct time with 1 pass. A bland moisturizer was used on the treatment area several times daily post-procedure for several days.

Issa and colleagues [45] ($n = 8$) found the combination of fractionated ablative RF (Pixel roller; in motion tip), topical retinoic acid 0.05% cream, followed by an acoustic pressure ultrasound (Legao System; Alma Lasers Ltd, Buffalo Grove, IL) resulted in 3 of 8 subjects with improvement from severe to moderate in striae severity, 2 of 8 with severe to mild improvement, and 2 of 8 with moderate to mild improvement of striae severity. RF treatment alone did not have an overall improvement of striae.

SUMMARY

Striae distensae have proven difficult to treat due to the 3-dimensional aspect of the scar and limitations of light-based therapies for darker skin types. The PDL laser has shown good efficacy in the treatment of striae rubra in skin types I to IV. Fractional lasers appear to provide the largest improvement in striae alba as a single treatment. Laser-assisted drug delivery is another approach that could improve treatment outcome. Combination therapies provided the largest benefit and should be the target of future research.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.yacs.2018.02.003>.

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Updates in Cellulite Reduction



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KEYWORDS

• Cellulite • Fibrous septae • Subcision • Cellfina • Cellulaze

KEY POINTS

- Cellulite refers to the dimpled appearance of the skin's surface most commonly found on the buttocks and thighs of women.
- Because its pathophysiology has long been misunderstood, it has historically been challenging to treat and durable treatment options have been lacking.
- More recently, treatment options have been developed targeting the fibrous septae that are now understood to play a key role in the pathogenesis of cellulite.
- Two novel devices, Cellfina and Cellulaze, offer a means to methodically transect these fibrous septae, and have been demonstrated to provide effective and lasting results.
- Cellfina offers several distinct advantages when compared with Cellulaze, including minimal patient downtime, fewer adverse effects, and results that are not user dependent but remain longer lasting.



Video content accompanies this article at www.advancesincosmeticsurgery.com.

INTRODUCTION

Cellulite describes the topographic dimpling and nodularity of the skin's surface that is most commonly found on the posterolateral thighs and buttocks of women. Although no precise epidemiologic data exist on its prevalence, it is thought to affect 80% to 90% of postpubertal women [1]. Despite being so common, many women view it unfavorably and as an imperfection. Although it is thought to be physiologic rather than pathologic, one should not overlook that it can cause significant distress. One study reported that 86.4% of participants believed that their cellulite negatively impacted their quality of life, with nearly one-third of them indicating that it had a moderate to severe impact [2]. Another

observational study found that 70% of patients being treated for cellulite believed that their cellulite hampered their lives “greatly” [3]. For these reasons, patients have spent billions of dollars on treatments that, until recently, provided minimal improvement at best.

ETIOLOGY

To truly appreciate the advances that have been made in the treatment of cellulite, it is valuable to briefly review the treatment modalities that have been trialed in the past. However even before doing so, one must first understand the pathophysiology of cellulite.

Disclosure Statement: Dr D.M. Robinson and Dr M.S. Kaminer are consultants to Merz. Dr D.J. Callaghan has no disclosures.

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Although the terms fat, adipose, and cellulite are sometimes used by patients interchangeably, it is important to realize their similarities and differences. Adipose tissue, also known as body fat, refers to a type of connective tissue comprised of adipocytes, collagen, blood vessels, and nerves. There are two main reservoirs for fat tissue in the body: visceral fat and subcutaneous fat. Subcutaneous fat, which is the target for body contouring procedures, such as liposuction and cryolipolysis, is often considered cosmetically undesirable but is not thought to contribute to obesity-related metabolic and cardiovascular diseases the same way visceral fat does [4]. Although subcutaneous fat makes up a component of cellulite, not all subcutaneous fat is cellulite. Cellulite specifically describes the nodularity and dimpling of the skin that results from underlying subcutaneous fat herniating between subcutaneous fibrous connective tissue. This is an important distinction because many treatments that are used to target subcutaneous fat have been trialed and failed for the treatment of cellulite. Patients may request a treatment that is known to target subcutaneous fat, such as cryolipolysis, to treat their cellulite. It is important to educate such patients on expectations, because although it may provide some benefit in reducing subcutaneous fat, it is unlikely to reduce the topographic changes that define cellulite.

This discrepancy in response to treatment is better elucidated by understanding the anatomic structure of subcutaneous tissue, and the changes that are seen in cellulite. Subcutaneous tissue is made up of two unique layers of adipose tissue, which are referred to as the superficial and deep layers. These layers are separated by a sheet of connective tissue primarily made up of collagen known as the superficial fascia. This superficial fascia runs parallel to the skin and muscle and fibrous bands of collagen then course orthogonally through this subcutaneous tissue from the undersurface of the dermis to the deep fascia adjacent to the muscle [5].

The observation that cellulite predominantly affects women may be explained in part because of differences in the anatomic structure of this superficial subcutaneous layer of fat. When compared with males, this superficial adipose layer in women is made up of larger fat-cell chambers, which can project upward into the dermis and change the overall appearance of the skin. Additionally, the fibrous bands that course vertically through the subcutaneous tissue run in a crisscrossing fashion in men, whereas they are oriented perpendicularly in women [5]. This difference is paramount because in males the orientation allows for the

downward tension created by these bands to be evenly distributed across the skin. In contrast, in females the orientation of the fibrous bands creates localized points of pressure that tether the dermis to the subcutaneous tissue. The combination of larger fat-cell chambers and localized points of tension in women leads to the rolling, dimpled appearance that is the hallmark of cellulite [5]. The sexual dichotomy of the orientation of fibrous septae and the resulting role in their pathogenesis of cellulite has been demonstrated using MRI [6].

Although it is clear that the formation of fibrous septae tethering the muscle to the dermis is integral for the formation of cellulite, the specific elements that contribute to the formation of these fibrous septae and ultimately the formation of cellulite has been a matter of debate for years. Although this debate still continues, it is now largely agreed to be an interplay of several complex factors including persistent low-grade inflammation, microvascular dysfunction and tissue edema, localized adipocyte hypertrophy, collagen denaturation, tissue laxity, and connective tissue fibrosclerosis [7,8].

TREATMENT OPTIONS TO DATE

Because these factors (persistent inflammation, microvascular dysfunction and tissue edema, localized adipocyte hypertrophy, collagen denaturation, and tissue laxity) have all been implicated in the formation of cellulite, they have also been the target of treatment of cellulite over many decades. However, years of research have also made it clear that once cellulite has manifested itself, targeting these factors implicated in the pathogenesis of cellulite has not provided clinically significant results. The diverse array of techniques that have been trialed in the past and the etiologic factor of cellulite being targeted is outlined in Table 1. These are presented as a reference and to acknowledge what has been tried in the past. Unfortunately, none of these treatments were shown to provide significant or durable results as demonstrated by two systemic reviews on the treatment of cellulite that included 73 and 67 studies, respectively [9,10]. As these reviews highlight, many of the included studies suffered from flaws including small sample sizes, lack of reporting of statistical significance, lack of a control group or randomization, or were nonblinded. Furthermore, the endpoints used in these studies are widely variable and have been subjective, inconsistent, fail to measure a valid indicator of cellulite severity, or lack extended follow-up.

TABLE 1
Past Treatment Modalities for Cellulite That Have Been Tried Without Clinically Significant, Reproducible, or Durable Results

Target	Treatment Modalities
Microvascular dysfunction and tissue edema	1. Methylxanthines (eg, caffeine) 2. Mechanical stimulation (manually or with the use of a device) 3. Acoustic wave therapy or extracorporeal shock wave therapy
Excessive subcutaneous adipose tissue	1. Weight loss 2. Cryolipolysis 3. High-intensity focused ultrasound 4. Low-level laser therapy (eg, wavelengths varying from 532 nm, 635 nm, and 808 nm) 5. High-powered laser therapy (eg, 1064-nm Nd:YAG) 6. Liposuction
Collagen denaturation and tissue laxity	1. Radiofrequency (unipolar, bipolar, or tripolar) 2. Infrared light

Abbreviation: Nd:YAG, neodymium:yttrium-aluminum-garnet.

ADVANCES IN TREATMENT

Fortunately, more recently two devices have emerged that have directly targeted the etiologic factor of cellulite, namely the fibrous septae. These fibrous septae are an important target because they form the dimpled appearance of cellulite by anchoring the skin to the subcutaneous tissue [6].

The most basic way to treat these fibrous septae is with manual subcision, in which individual septae are dissected with a needle or blade. A retrospective observational study by Hexsel and Mazzuco [11], which included 232 patients treated with subcision, found that 78.87% of them were satisfied with their improvement in cellulite, whereas an additional 20.25% were partially satisfied. Similar to other studies involving cellulite, this study was limited by the fact that it did not include a control and the results were subjective. However, it improved on other studies by including a longer follow-up period than most other studies involving cellulite and illustrated that 23 (9.91%) patients who were followed for more than 2 years maintained improvement [11].

In light of these positive results, two devices aimed to automate the process were developed: Cellfina (Ulthera/Merz, Mesa, AZ) and Cellulaze (Cynosure, Inc, Westford, MA). These two devices have been demonstrated in high-quality trials to provide not only statistically significant but also sustainable improvement in the appearance of cellulite.

Cellfina is a device that uses vacuum-assisted tissue guidance to administer anesthesia and release fibrous septae. The vacuum chamber lifts and fixes tissue for anesthetic delivery and tissue release via a microblade that ensures precise control of the depth and area of tissue release. This automated process uses a motor module to control the rapidly reciprocating blade through predefined paths at user-selected depths of either 6 mm or 10 mm, which produces repeatable results that have proven to be significant and durable [12,13]. Unlike other previous treatments for cellulite, these results are seen with just one treatment.

Kaminer and colleagues [12] studied 55 women who underwent a single treatment and found that at 1 year, 94% of subjects had improvement of one grade or more as evaluated by blinded observers using an objective, validated cellulite severity scale (CSS). The mean change in CSS at 1 year was two points ($P<.0001$). In opposition to most other studies published on treatment of cellulite, the subjects were followed over time, and at 3 years post-treatment, 91.1% of subjects had sustained improvement as determined by the same objective CSS. At the 2-year mark patient satisfaction reached 96%, the highest level of any timepoint of the study and was sustained at 93% at 3 years [13,14]. Given these objective results, it is concluded this vacuum-assisted subcision device provides an acceptable, reproducible, and durable treatment option for cellulite with high patient satisfaction (Fig. 1). In light of these data, the Food and Drug Administration (FDA) has cleared Cellfina for the treatment of cellulite for results that last up to 3 years, the longest duration of any device cleared by the FDA.

Alternative to subcision with a needle or blade, Cellulaze is a long-pulsed 1440-nm energy device that is inserted subcutaneously using a cannula and thermally subcises septae via a side-firing system. The laser uses a special fiber that distributes roughly half of its energy perpendicular to the fiber axis and the other half along the fiber axis. In addition to transecting the fibrous septae, this provides the additional benefit of heating the hypodermal adipocytes, which results in lipolysis. The energy also denatures adjacent collagen, subsequently

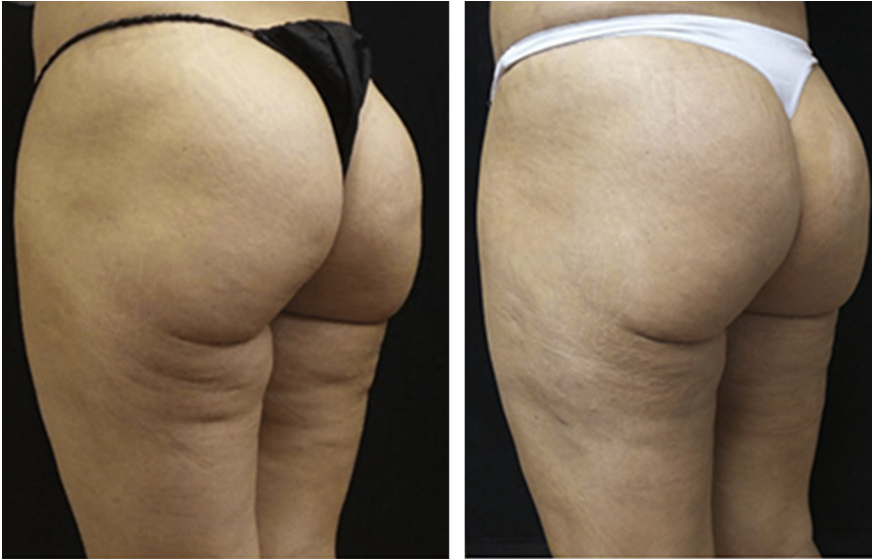


FIG. 1 Before and after photos of deep cellulite lesions on the posterolateral thighs treated with Cellfina, showing clear resolution.

stimulating neocollagenesis, dermal thickening, and tissue tightening. As opposed to other laser devices that attempted to treat cellulite by administering energy external to the skin, this minimally invasive device delivers the energy internally allowing the subcutaneous tissue to be targeted more selectively [15–18].

In a study of 25 women with this device, independent assessments showed that 80% of subjects demonstrated mild improvement at 6 months and 64% of subjects showed sustained mild improvement at 2 years, although statistical significance was not reported [15]. DiBernardo and colleagues [16,17] also reported at least a one-point improvement in dimple count or contour irregularity in 96% of treated areas at 6 months, which was sustained in 90% of treated areas at 1 year. Given these data, the FDA has cleared Cellulaze for the treatment of cellulite for results that last up to 9 months.

Although both devices have been cleared by the FDA and have been shown in clinical trials to be effective for the treatment of cellulite, there are important differences between the two, which are highlighted in Table 2.

TREATMENT TECHNIQUE FOR CELLFINA AND CELLULAZE

Preoperative Planning (Identical to Both Treatment Options)

- Before treating any patient for cellulite, it is important to do a thorough pretreatment assessment

and to clearly set goals and expectations. It is crucial to understand what the patient perceives to be cellulite, because some may consider it to be any excess bulge of adipose tissue or area with tissue laxity. Treatment of cellulite, skin laxity, and lipodystrophy are not one and the same.

- Pretreatment assessment includes determining any prior history of surgical or nonsurgical treatment of cellulite or subcutaneous adipose tissue, trauma, peripheral vascular disease, lymphatic disease, keloids/scarring, or acute infections.
- Data including weight and body mass index should be recorded. Thigh circumference is used to assess response to treatment but has low reliability and a change in circumference does not always correspond to a change in cellulite severity.
- A physical examination should be performed with patients in a standing and supine position. Cellulite that is not visible while lying down may be present while standing. Manipulation of the tissue, either by asking the patient to contract muscles to accentuate dimples or use the pinch test to force adipose upward into the reticular and papillary dermis makes cellulite more appreciable and easier to assess [19]. The use of tangential lighting in different positions can also help cast shadows on topographic skin changes that are more

TABLE 2
Clinically Relevant Differences Between Cellfina and Cellulaze

	Cellfina	Cellulaze
Method of action	Vacuum-assisted tissue capture that uses a microblade to subcise fibrous septae	1440-nm Nd:YAG wavelength laser with side-firing fiber that subcises fibrous septae, leads to lipolysis, and also stimulates collagen deposition
Invasiveness	Minimally invasive, only requires small points of entry with a 0.45-mm microblade	Minimally invasive, but requires several larger incisions (1 mm) for the laser cannula to be introduced
Anesthesia required	No systemic anesthesia is required, and a significantly lower volume of tumescent anesthesia is required because the device automates the process; this also allows for this step to be more easily delegated to a nurse or physician extender	Typically requires light oral anesthesia (with a benzodiazepine and narcotic pain medication) Also requires traditional tumescent anesthesia, which necessitates greater experience and expertise by the clinician who is administering it, and the greater volume leads to patients experiencing more leaking after the procedure
Patient downtime	Zero, because of the lack of systemic sedation the patient can drive home and return to work immediately	Because of the use of oral anesthesia, the patient cannot drive home, and typically should plan on missing work for 1–3 d after the procedure
Adverse effects	Mild, typically resolve with no sequelae	Greater risk for seromas, bruising, and hemosiderosis-induced hyperpigmentation
Procedure time	After anesthesia is administered, the procedure time is roughly 20–30 min	After anesthesia is administered, the procedure time typically takes at least 60 min
User dependence	Extremely minimal learning curve and results are not user dependent because the automated device allows for reproducible results	Steeper learning curve, surgeon technique is important, and results are technique dependent
Durability of results	FDA-approved for results that last up to 3 y, literature reporting on the durability results at 3 y, and clinical practice has shown results lasting beyond 5 y [13]	FDA-approved for results that last at least 9 mo, no literature reporting results beyond 2 y [15]

Abbreviation: Nd:YAG, neodymium:yttrium-aluminum-garnet.

difficult to assess using the naked eye and direct lighting.

- In terms of patient selection, these procedures are most successful for patients that have deeper linear or dimpled depressions giving a “cottage cheese” or “mattress” appearance. Although Cellfina provides the ability to treat lesions at a depth of 6 mm and 10 mm, some patients present with even more superficial, smaller surface changes leading to an “orange peel” appearance. These patients may not be as satisfied by treatment with Cellfina or Cellulaze because the target of these devices is deeper. Additionally, patients may also be poor candidates if they present with significant laxity, sagging of the skin, or a volume deficiency or excess. Even if the appearance of their cellulite is improved by reducing
- any dimpling, they may still be unhappy. These patients may receive more benefit from treatment with other body contouring procedures, such as liposuction, cryolipolysis, fat transfer, or (off label) dermal fillers. It is important to get a firm understanding of what bothers the patient so they are counseled appropriately on their expectations.
- It is extremely important to obtain pretreatment pictures, ideally in several patient positions and with different lighting, because these are crucial to assess the patient at follow-up visits. The authors prefer to take at least five photographs with one from behind, and the patient turned in each direction at 45° and 90°, which allows the lesions to be better visualized. Although a CSS has been developed and validated, this is more useful for following patients in the setting

of clinical trials. For individual patients, photographic documentation is paramount.

Cellfina

- Preparation and patient positioning
 - Select the areas for treatment and mark them with a surgical pen with the patient standing. A single line should be made for smaller lesions (roughly a 1–1.5 cm or less), whereas larger lesions should be circled. This difference is important during the procedure, as discussed later. It is vital to mark the sites before anesthesia because the tumescent anesthesia distorts the treatment area.
 - In addition to pretreatment photographs, the authors take an additional set of photographs after marking the patient.
 - The patient should lie comfortably in the prone position with the treatment area exposed.
 - Clean the areas with an antiseptic scrub.
- Procedural approach (Video 1)
- Connect the anesthesia needle assembly (22 gauge) to the device and administer tumescent anesthesia. The authors prefer to use a mixture of 1-L 0.9% normal saline, 50-mL 0.1% lidocaine, 12.5-mEq/L sodium bicarbonate, 1-mL 1:100,000 epinephrine, and 1-mL Kenalog-10.
 - After preparing the patient as outlined previously, connect the vacuum suction and acquire the target tissue into the chamber recess and administer a 6 to 8 mL of tumescent fluid per anesthetic delivery track.
 - Repeat the tissue acquisition and infiltration sequence until all predetermined, marked locations are infiltrated being careful not to exceed the total allowable anesthetic volume based on weight.
 - Allow sufficient anesthetic dwell time, which is approximately 20 minutes.
 - Attach the release guidance platform to the vacuum chamber.
 - Decide on release depth of 6 mm or 10 mm, acquire the target tissue into the chamber recess, and use the device to provide controlled release of the dimple. The authors treat almost all lesions at a depth of 6 mm, unless there are two lesions immediately adjacent to one another, at which point it is important to alternate depths of 6 and 10 mm which, in published studies, brings the risk of developing a seroma to virtually zero [12].

- For larger lesions, which were previously demarcated with a circle, position the lesion into the first treatment window, apply suction, insert the microblade until it is aligned with the first track, and then gently sweep the blade back and forth for a total of four passes (Fig. 2A).

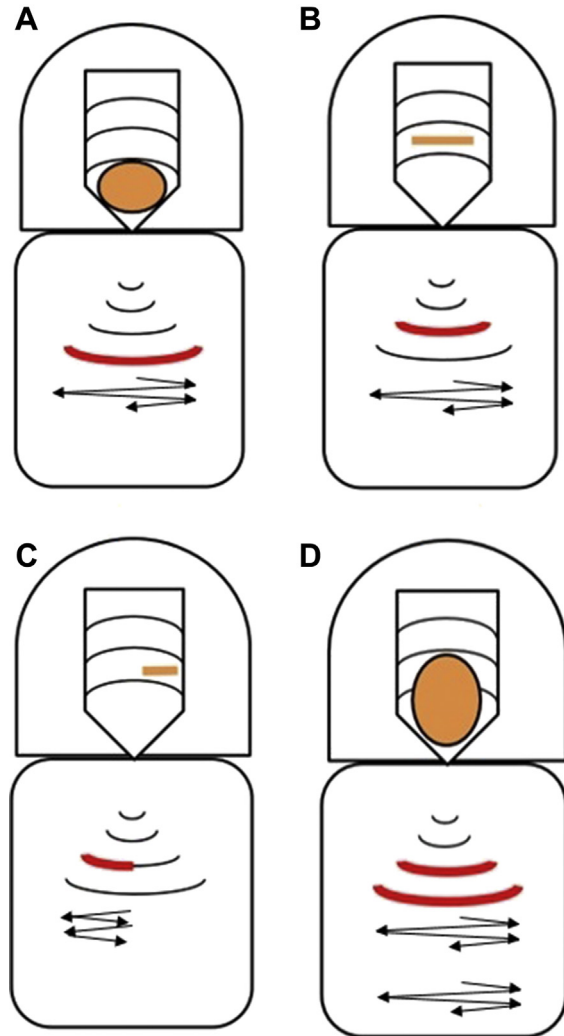


FIG. 2 How to align Cellfina over cellulite lesions. (A) If a lesion is large enough to fill the first window, treat with four passes in the first track. (B) If a lesion fills the second window, treat with a total of four passes in the second track. (C) For smaller lesions, align them with the edge of the second track, and then treat with four passes in the corresponding half of the second track (which is on the opposite side of the lesion). (D) For lesions that fill both the first and second window, treat with a total of four passes in the first and second track.

- For smaller lesions, which were previously demarcated with a line, align them with the second treatment window and repeat the previously described process, but extend the microblade to the second track (Fig. 2B).
 - For even smaller lesions, approximately half of the size of the second treatment window, treat them by using only half of the track. Do so by sweeping the blade back and forth but staying on the side of the track opposite to the lesion (Fig. 2C).
 - If there is a single lesion that is large enough to encompass the first and second windows, treat it using four passes in the first followed by the second window (Fig. 2D).
 - For lesions that are in close vicinity to one another, but not immediately adjacent (which necessitates changing the depth of the microblade), carefully align the lesion to the edge of the window so that the microblade does not extend beyond this area and potentially connect with another treatment area.
 - Each lesion should be treated in this process individually, which reduces the risk of developing a seroma.
 - Immediate post-procedure care
 - After the procedure, massage the tissue toward the microblade incision sites, which expels any remaining tumescent anesthesia.
 - The treated areas should be cleaned, and then an emollient, such as petroleum jelly, should be applied followed by ABD Pads and then bandaged with a midstrength compression dressing.
 - Rehabilitation and recovery
 - Patients should wear compression garments as often as possible for 1 week.
 - Potential complications and management
 - The most common adverse effects include bruising, fluid accumulation, areas of palpable softness or firmness, tingling, and soreness [12]. These are managed with over-the-counter pain medications, pressure, and ice packs. At 2- and 3-year follow-up, there were no reports of sustained pain, treatment effects, or adverse effects [13,14].
- Cellulaze**
- Preparation and patient positioning
 - Select the areas for treatment and mark them with a surgical pen with the patient standing. Both dimples and raised areas should be marked out and the target area should be divided into square, 3×3 or 5×5 cm sectors because each sector is treated individually based on if it contains a raised area or a depression.
 - After marking, the patient should lie comfortably with the treatment area exposed.
 - Clean the area with an antiseptic scrub.
 - Procedural approach
 - The treatment area should first be treated with traditional tumescent anesthesia.
 - Two to four 1-mm incisions should be made for introducing the laser cannula, and the cannula should be gently positioned below the skin surface.
 - To treat raised sections, position the fiber in the down position 1 cm to 2 cm beneath the skin and move it back and forth in a fanlike pattern, delivering 300 J for a 3×3 cm sector or 600 J for a 5×5 cm sector. The treatment end point is the number of joules of energy delivered to the tissue, rather than the skin surface temperature.
 - To treat depressed areas, position the fiber in a horizontal position and move the fiber in the same fanlike pattern and in the same plane as the previous step. An end point should be loss of resistance as the cannula passes through the tissue, which indicates that the septa no longer connect the dermal and muscle layers.
 - Finally, position the fiber 2 mm to 3 mm below the skin surface and position it up, and treat all sectors with the same fanlike pattern to smooth the dermal-hypodermal layer.
 - Remove the fiber and gently massage the treated areas toward the incision site to gently remove any liquefied adipocytes.
 - Immediate post-procedure care
 - After the procedure, the treated areas should be cleaned and bandaged with a compression dressing.
 - Rehabilitation and recovery
 - Patients should wear compression garments as often as possible for 2 to 3 weeks.
 - Potential complications and management
 - The most common adverse effects are all mild and include discomfort, bruising, swelling, and numbness, which are managed with over-the-counter pain medications, pressure, and ice packs. These all typically resolve within 3 months, and a multicenter study of 57

patients found no adverse events reported at 12 months [16,18].

- Exudative collections or seromas may rarely be observed and may require intermittent aspiration.

SUMMARY

Cellulite is a condition that negatively impacts quality of life, and therefore has prompted researchers to seek a reliable treatment option for years. Although several treatment options have been trialed over the years, until recently a durable, reproducible solution remained elusive.

Fortunately for those individuals negatively affected by cellulite, a better understanding of the role fibrous septae play in the pathogenesis of cellulite has allowed several treatment options to emerge that have shown objective, significant, and durable results. Cellfina and Cellulaze use the concept of subcision and are FDA-cleared for the treatment of cellulite for results that last up to 36 months and 9 months, respectively. Cellfina provides clinicians with an automated, reproducible method of doing so that affords patients durable results while minimizing downtime or adverse effects.

In addition to Cellfina and Cellulaze, other treatment options to address the septae may emerge, such as Xiaflex (Endo International, Malvern, PA), a collagenase produced by *Clostridium histolyticum* that has demonstrated statistically significant improvement in the appearance of cellulite in a 28-day study, but needs to be studied further to assess if the benefit is sustainable [20].

One cannot dismiss the other proposed pathophysiologic mechanisms of cellulite, and in time a better understanding of them may provide patients with a way to diminish the formation of cellulite before it is clinically apparent. At this time, however, any treatment that hopes to provide durable and reliable benefit to patients should be aimed at addressing the fibrous septae responsible for its clinical appearance.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jyacs.2018.02.006>.

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Current Evidence in Nonsurgical Fat Reduction



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KEYWORDS

• Nonsurgical • Fat reduction • Cryolipolysis • Radiofrequency • Ultrasound • Deoxycholic acid

KEY POINTS

- Despite the popularity of liposuction, the demand for nonsurgical fat reduction continues to steadily increase for those patients unwilling to undergo a surgical procedure.
- Cryolipolysis, chemical lipolysis, and thermal modalities, such as ultrasound and radiofrequency, have demonstrated the ability to effectively reduce excess subcutaneous adipose tissue, while minimizing risks, discomfort, and downtime.
- Nonsurgical fat-reduction modalities vary greatly because some require a single treatment, whereas others require multiple treatments and maintenance sessions.
- Future studies using standardized outcome measures should be considered to accurately compare current nonsurgical fat-reduction modalities.



Video content accompanies this article at www.advancesincosmeticsurgery.com.

INTRODUCTION: NATURE OF THE PROBLEM

Americans spent more than 15 billion dollars in 2016 on surgical and nonsurgical procedures [1]. The American Society for Aesthetic Plastic Surgery 2016 Cosmetic Surgery National Data Bank Statistics reported that liposuction remained the most popular surgical procedure with 414,335 procedures performed in 2016, a 4.6% increase from 2015 [1]. Liposuction is still considered the gold standard for treatment of excess subcutaneous fat; however, because of its invasive nature it retains risks, discomfort, and downtime [2–5]. Despite the popularity of liposuction, the demand for nonsurgical fat reduction continues to steadily increase for those

patients unwilling to undergo a surgical procedure. The American Society for Aesthetic Plastic Surgery 2016 Cosmetic Surgery National Data Bank Statistics also reported that there were 169,695 nonsurgical fat-reduction procedures performed in 2016, a 5.6% increase from 2015 [1]. Cryolipolysis, chemical lipolysis, and thermal modalities, such as ultrasound and radiofrequency, have demonstrated the ability to effectively reduce excess subcutaneous adipose tissue (Table 1), while minimizing risks, discomfort, and downtime [2,3,6–8]. For those patients desiring to reduce excess subcutaneous fat without the risks, discomfort, and downtime of a surgical procedure, nonsurgical fat-reduction modalities have shown to be an effective

Disclosure Statement: The authors have nothing to disclose.

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TABLE 1
Nonsurgical Fat-Reduction Modalities and Mechanisms of Action

Cryolipolysis	Cold-induced adipocyte apoptosis [2,5,9–12]
Chemical lipolysis (deoxycholic acid)	Lipolysis through destruction of adipocyte cell membrane [2,7,13,14]
Radiofrequency	Apoptosis through repeated adipocyte damage [2,15]
High-intensity focused ultrasound	Coagulative necrosis of adipocytes [2,16–19]

therapeutic option. Cosmetic practices that familiarize themselves with advances in nonsurgical fat-reduction modalities can offer the cosmetic patient various options for treating excess subcutaneous fat [8].

CRYOLIPOLYSIS (CoolSculpting)

Cryolipolysis was introduced as a novel nonsurgical fat-reduction technique by Manstein and colleagues [2,6] in 2007 and is one of the most recent procedures for nonsurgical fat reduction to become popularized. CoolSculpting (ZELTIQ Aesthetics, Pleasanton, CA, USA) is the only Food and Drug Administration (FDA)-approved cryolipolysis device. Currently more than 4 million CoolSculpting treatments have been performed worldwide [20]. Cryolipolysis has the ability to selectively destruct adipose tissue through controlled cooling [21]. The initial development of cryolipolysis was based on the observations of cold-induced fat reduction in the cheeks of children termed “popsicle panniculitis” [2,5,6]. The approach to cryolipolysis uses the observation that lipid-rich cells have a higher susceptibility to cold injury in comparison with water-rich cells, which allows adipocytes to be selectively targeted while sparing the surrounding tissue, such as vessels, nerves, muscles, and skin, [2,6,21]. Cryolipolysis is performed by applying a cup-shaped applicator with two cooling panels and initiating vacuum suction to draw target tissue between the cooling panels [2,11]. A cryolipolysis treatment session typically takes 60 minutes and decreases the temperature of target tissue drawn into the applicator to approximately 0°C [2,21]. Within the adipocytes, triglycerides crystallize and initiate the inflammatory process of adipocyte apoptosis, panniculitis, and subsequent elimination of adipocytes by macrophage phagocytosis, which is

clinically observed as a reduction of fat in the treated area [21]. The process begins 2 to 14 days following cryolipolysis treatment and persists for at least 4 months [9]. Cryolipolysis received FDA clearance in 2010 for flanks, 2012 for abdomen, 2014 for thighs, and 2015 for submental region [5]. Safety and efficacy of cryolipolysis for nonsurgical fat reduction has been established through numerous clinical studies.

Preprocedure Planning

Proper patient selection is necessary in patients seeking treatment with CoolSculpting. During visual assessment identify how fat naturally presents on the patient’s body and note any asymmetries [22]. During physical assessment perform a skin pinch test to determine if the tissue is pliable and if there is sufficient fat to be pulled into the applicator cup [22]. Excessive skin laxity, scar tissue presence, former aesthetic procedures in treatment area, and any asymmetries need to be considered and discussed with the patient before treatment to prevent an undesirable aesthetic outcome following CoolSculpting treatment. Obtaining baseline weight, circumferential measurements, and photographs are also an important consideration in preprocedure planning. Patients should understand that weight gain can contribute to an increase in subcutaneous fat in the treatment area and elsewhere. The amount of areas to be treated and the number of treatment sessions required varies among patients, which directly affects cost and should be discussed before treatment. Results are typically seen about 2 months following treatment and continue to improve for up to 4 to 6 months [23].

Patients should be prepared to anticipate common adverse effects following treatment. The most common adverse effects following treatment with CoolSculpting include erythema, edema/swelling, hematoma/bruising, blanching, pain, induration, pruritis, skin sensitivity, and paresthesia, which in most cases resolve within a few weeks after treatment [6,23]. It is also important to discuss the limitations of CoolSculpting because it is limited to the treatment of unwanted fat in target areas and is not a weight-loss solution for obese patients [23]. Setting realistic expectations in regards to cost, number of treatments, outcomes, and limitations is essential to patient satisfaction.

Preparation and Patient Positioning

The appropriate applicator for the treatment area is selected based on the need for debulking or sculpting (Table 2). The CoolMax applicator is ideal for large-volume reduction to debulk [22]. The CoolCore,

TABLE 2
Selection of Appropriate Applicator

CoolMax	Debulking: ideal for large-volume reduction
CoolCore	Sculpting: used most commonly for abdomen
CoolCurve	Sculpting: ideal for curves, used commonly in flanks
CoolFit	Sculpting: ideal for longer, vertical areas of fat

Data from Ref. [22].

CoolCurve+, and CoolFit applicators are ideal for sculpting [22]. Identify and mark the focal point of the target area with an “X,” then mark the treatment area using the appropriate applicator template [22].

Procedural Approach

Position a protective transparent gel pad over the marked treatment area (advise the patient that it will feel cold) then apply the protective transparent gel pad and smooth it to the skin to protect it from cold injury [11,24]. Apply a disposable liner to the applicator cup of the handpiece to prevent coupling gel from being suctioned into the vacuum line [11]. Initiate vacuum suction and position the applicator cup over the marked treatment area (advise the patient that they will feel a strong pinch and discomfort that will last approximately 5–7 minutes), then place the applicator cup onto the skin of the treatment area and allow the vacuum to suction the tissue into the applicator cup [11]. Position a Boppy pillow around the applicator cup to stabilize the handpiece and increase patient comfort. Once the handpiece is properly placed and stabilized initiate the coolant to begin the 60-minute treatment cycle [11]. When the 60-minute treatment cycle is complete, remove the Boppy pillow, stop the vacuum, and break the suction manually with fingertips to remove the handpiece. Remove the transparent protective gel pad from the treatment area (Video 1).

Immediate Post-Procedural Care

Immediately following removal of the handpiece and transparent protective gel pad the tissue is indurated and erythematous, commonly referred to as a “butter stick” appearance [11,25]. Manual massage of the treatment area should be performed for 2 minutes to soften and rewarm the tissue [11]. Post-treatment manual massage has demonstrated the effect of increased fat

reduction in studies and is recommended for optimal results.

Rehabilitation and Recovery

Common adverse effects following cryolipolysis treatment include sensitivity, pain, bruising, swelling, erythema, and numbness [2,6,12,20,26]. Patients experiencing any of these adverse effects should be reassured that they are transient and typically resolve within a few days to weeks following treatment [2,6,12,20,26].

Clinical Results in the Literature

In the United States, CoolSculpting has FDA clearance for the treatment of visible fat bulges in the submental area, thigh, abdomen and flank, along with bra fat, back fat, underneath the buttocks (also known as “banana roll”), and upper arm in patients with a body mass index of 30 or less using cryolipolysis [20,26]. Currently there are more than 70 CoolSculpting clinical studies, reviews, and publications in the literature (Table 3).

Potential Complications/Risks/Benefits/Limits

Potential complications and risks of cryolipolysis are rare and include paradoxical adipose hyperplasia and postinflammatory hyperpigmentation. Paradoxical adipose hyperplasia is a rare delayed complication and is estimated to have an incidence of 0.0051% or about 1 in 20,000 patients [21]. Postinflammatory hyperpigmentation has a reported incidence of less than 0.003% or about 1 in 33,000 patients. A prospective study of 53 patients by Adjadj and colleagues [9] reported an 8.33% incidence of postinflammatory hyperpigmentation following cryolipolysis on saddlebags or about 1 in 12 patients. The significant difference in the incidence of postinflammatory hyperpigmentation is concerning. It was noted in a discussion by Kilmer [24] that the device used in the study was not CoolSculpting, but a French replicate cryolipolysis device that does not have FDA clearance and has not established safety and efficacy in clinical studies. Providers must understand that replicate and original devices are not interchangeable [24]. The purchase of inexpensive replicate devices without FDA clearance can put the patient and physician at an unacceptably increased level of risk [24].

The benefits of cryolipolysis include noninvasive, ability to significantly reduce fat, limited downtime, high patient satisfaction rate, and minimal to no risk of complications [8]. The limits of cryolipolysis include disposable applicator cost, inability to precisely control fat reduction, need for treatment area fat to

TABLE 3
CoolSculpting Clinical Results

First Author, Year	Outcomes
Bernstein, 2013	Treated flank demonstrated persistent fat reduction 2 y following CoolSculpting treatment.
Bernstein, 2013	Treated flank demonstrated persistent fat reduction 5 y following CoolSculpting treatment.
Bernstein, [5] 2016	Demonstrated that cryolipolysis reduces subcutaneous fat for at least 6 and 9 y post-treatment.
Bernstein & Bloom [11], 2017	Caliper measurements demonstrated a mean fat layer reduction of 2.3 mm. 3-D imaging revealed a mean fat volume reduction of 4.82 cm ³ , skin surface area reduction of 1.29 cm ² , and fat thickness reduction of 3.77 mm. 93% of patients reported satisfaction with treatment results.
Boey, 2014	Average fat layer reduction measured by ultrasound was 68% greater on massaged side at 2 mo, and 44% greater at 4 mo.
Brightman, 2011	Average reduction of 2.4 cm in 3-D imaging measurements of circumferential abdomen/flank areas.
Coleman, 2009	Average fat layer reduction measured by ultrasound was 20.4% at 2 mo and 25.5% at 6 mo. Nerve biopsy demonstrated no long-term changes to nerve structure.
Dierickx, 2013	94% of patients showed fat reduction in caliper measurements, with a 23% fat reduction in comparison with control site at 3 mo.
Dover, 2009	Average fat layer reduction measured by ultrasound was 22.4% at 4 mo, 100% of subjects demonstrated fat layer reduction.
Dover, 2011	80% of patients reported that they were happy with their treatment results at 6 mo.
Ferraro, 2012	Fat circumference median reduction: 6.86 cm in abdomen, 5.78 cm in thighs, 2.75 cm in arms, 5 cm in buttocks, and 2.25 cm in ankles. Average caliper measurement reduction: 4.5 cm in abdomen, 3.6 cm in thighs, 2.1 cm in arms, 4 cm in buttocks, and 1 cm in ankles. Lipid and liver function tests remained within normal limits.
Garibyan, 2014	56.2 mL average fat reduction in 3-D imaging measurements. 14.9% average fat reduction in caliper measurements at 2 mo following treatment.
Jalian et al [21], 2014	Paradoxical adipose hyperplasia as a gradual nontender growth of tissue at treatment site, stabilizing at 5 mo.
Kaminer, 2009	Reviewers were able to differentiate between baseline and post-treatment photographs in 89% of evaluated cases.
Klein, 2009	No significant changes were observed for any lipids or liver test at any point during the 12 wk following treatment.
Klein et al [27], 2017	Multiple, same day cryolipolysis treatments for subcutaneous fat reduction demonstrated safety and did not affect serum lipid levels or liver function tests. No treatment-related adverse effects were reported.
Lee, 2013	Fat reduction efficacy in cryolipolysis-treated site was 19.55% compared with 28.2% in radiofrequency-treated site. Results were not statistically significant. No significant difference in lipid levels or fasting blood glucose levels at 1, 4, or 12 wk following treatment.
Pinto, 2012	Average fat reduction by caliper measurement was 19.7% for 1 treatment and 28.5% for 2 treatments at 40-d follow-up.
Riopelle, 2009	No significant changes in lipid or liver function tests at 1, 4, 8, or 12 wk following treatment in patients with evident fat reduction measured by ultrasound.
Rosales-Berber, 2009	79% of subjects reported efficacy within 2–4 mo following treatment.

(continued on next page)

TABLE 3
(continued)

First Author, Year	Outcomes
Sasaki, 2014	Average fat reduction by caliper measurement was 21.5% in abdomen. Average fat reduction by ultrasound measurement was 19.6% in abdomen.
Shek, 2012	Average fat reduction by caliper measurement was 14.7%.
Shek, 2012	Average fat reduction by caliper measurement following first treatment was 14% in abdomen and 13.4% in love handle. Average fat reduction by caliper measurement following second treatments was an additional 7.2% in abdomen and 4.3% in love handle.
Stevens, 2013	CoolSculpting demonstrated consistent growth in procedure volume with an 823% increase in treatments from 2010 to 2012.
Zelickson et al [28], 2009	Demonstrated significant reduction in superficial fat layer without damage to overlying skin. Evaluation of lipids 3 mo following treatment demonstrated that cholesterol and triglyceride levels remained normal.

Abbreviation: 3-D, three-dimensional.

Data from Refs. [5,6,8,10,11,27,28].

appropriately fit into the applicator, potential need for multiple treatments, ability to expose underlying defects, and inability to tighten skin [8].

Management

There is no evidence that paradoxical adipose hyperplasia spontaneously resolves and currently the only corrective treatment options are liposuction or excision [21]. The treatment of postinflammatory hyperpigmentation is often a difficult and prolonged process. The current treatment guideline for first-line therapy is triple combination therapy consisting of topical hydroquinone, topical retinoids, and topical corticosteroids [29]. Patients experiencing postinflammatory hyperpigmentation should be advised that the process typically takes 6 to 12 months or longer to resolve [29].

CHEMICAL LIPOLYSIS (DEOXYCHOLIC ACID/KYBELLA)

Deoxycholic acid, which is commercially known as Kybella (Allergan plc, Irvine, CA, USA), is a first-in-class injectable drug and is currently the only injectable drug available for chemical lipolysis [8,13,30]. Kybella is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults [30]. Clinical studies have demonstrated the ability of deoxycholic acid to induce lipolysis through disruption of the adipocyte cell membrane [8,13]. Subcutaneous injection of deoxycholic acid into fat induces fat necrosis, causing inflammation resulting in macrophage infiltration, fibroblast recruitment, and neocollagenesis

[14]. Although there have been clinical studies demonstrating that deoxycholic acid is rapidly absorbed on injection into submental fat and abdominal fat, Kybella is currently FDA approved for injection into submental fat only [8,13,30]. The safety and efficacy of injecting Kybella into subcutaneous fat other than submental fat has not been established [30].

Preprocedure Planning

Proper patient selection is necessary in patients seeking treatment with Kybella. The provider needs to screen patients for differing potential causes of submental convexity or fullness, such as thyromegaly and cervical lymphadenopathy [30]. A simple skin pinch test between thumb and index finger is performed to assess submental fat and determine if there is adequate submental fat for treatment with Kybella [31]. Excessive skin laxity, platysmal band prominence, scar tissue presence, and any asymmetries need to be considered and discussed with the patient before treatment to prevent an undesirable aesthetic outcome following reduction of submental fat [30,31]. Obtaining baseline weight and photographs are also an important consideration in preprocedure planning. Patients should understand that weight gain can contribute to an increase in submental fullness. The amount of drug administered and the number of treatment sessions required varies among patients, which directly affects cost and should be discussed before treatment. Most patients receive between 4 and 6 mL (two to three vials) of Kybella per treatment and require between 2 and 5 treatments to achieve aesthetically desirable outcomes [7,8,13,14]. Adipocytolysis and the inflammatory

process following treatment is 28 days to resolution, therefore treatments are recommended to be performed at no less than 4-week intervals [7,14]. As submental fat decreases following treatment, less Kybella may be required at each successive treatment, so it is important to continue to assess for adequate submental fat at each visit before treatment [13].

Patients should be prepared to anticipate common adverse effects and downtime following treatment. The most common adverse effects following treatment with Kybella are edema/swelling, hematoma/bruising, pain, numbness, erythema, induration, and paresthesia, which in most cases resolve within 7 to 14 days [8,30]. It is also important to discuss the limitations of Kybella because it is limited to treatment of the submental region only. Subcutaneous fat reduction of surrounding areas of the neck and jawline can only be achieved with liposuction. Setting realistic expectations in regards to cost, number of treatments, downtime, outcomes, and limitations is essential to patient satisfaction.

Preparation and Patient Positioning

Before treatment the patient's lower face and anterior neck should be cleansed with an appropriate topical anti-septic [32]. Topical anesthetic (apply before marking) or injectable local anesthetic (apply following marking) may be administered before Kybella treatment to increase patient comfort [32,33]. Mark the anterior, posterior, and lateral borders of the submental fat compartment, then mark a "no-treatment zone" to decrease the potential for marginal mandibular nerve injury [32]. Apply skin-marking grid firmly onto skin (grid pattern facing down) and thoroughly wet paper backing with sterile water-soaked gauze or cotton ball [32]. Wait 15 seconds and then peel off the skin-marking grid [32]. Remove any dots outside of the previously marked treatment area using isopropyl alcohol [32]. Count the number of dots remaining to determine the dose of Kybella (each dot is equivalent to 0.2 mL of Kybella) and then prepare the appropriate number of syringes by drawing 1 mL of Kybella into sterile 1-mL syringes using a large-bore needle and replacing with a 30-gauge 0.5-inch needle [32]. Do not mix or dilute Kybella [32]. Apply ice or cold pack for 5 minutes before injecting Kybella [32].

Procedural Approach

Pinch the preplatysmal fat between thumb and index finger and inject perpendicular to the skin inserting approximately half the length of the needle and inject 0.2 mL of Kybella adjacent to each dot (to avoid unintentional tattooing of the skin) [32]. Do not inject

Kybella within 1 to 1.5 cm below the inferior border of the mandible to avoid marginal mandibular nerve injury [32]. Do not inject Kybella into the platysma or postplatysmal fat to avoid dysphagia [32]. Do not inject Kybella into the dermis or withdraw the needle during injection to avoid skin ulceration (Video 2) [32].

Immediate Post-Procedural Care

Immediately post-procedure apply ice or cold pack to the treated area for 5 to 15 minutes. Using isopropyl alcohol, remove the dots and cleanse the treated area. Instruct the patient to smile and swallow to assess for marginal mandibular nerve injury and dysphagia [32]. Reiterate post-procedure expectations and encourage the patient to schedule their next Kybella treatment before leaving the office [32].

Rehabilitation and Recovery

Post-procedure expectations following treatment with Kybella include edema/swelling, hematoma/bruising, pain, numbness, erythema, induration, and paresthesia, which typically resolves within 7 to 14 days [8,30]. Ice or cold packs, compression, and/or analgesics may be used as needed for patient comfort during recovery [33].

Clinical Results in the Literature

Kybella was given FDA approval based on the evidence of two clinical trials that enrolled 1022 participants (Table 4) [34]. The trials were conducted at 70 clinical sites throughout the United States and Canada [34].

TABLE 4
Chemical Lipolysis Clinical Results

First Author, Year	Outcomes
Humphrey et al [14], 2016	66.5% achieved a composite improvement of 1 or more grades. All treated subjects achieved submental volume reduction confirmed by MRI, improvement in psychological impact of submental fat, and satisfaction with treatment.
Jones et al [7], 2016	70% achieved a composite improvement of 1 or more grades. All treated subjects achieved submental volume reduction confirmed by MRI, improvement in psychological impact of submental fat, and satisfaction with treatment.

Data from Refs. [7,14].

Potential Complications/Risks/Benefits/Limits

Potential complications of Kybella treatment are marginal mandibular nerve injury and dysphagia. Marginal mandibular nerve injury was reported in approximately 4% of all clinical trial patients. Dysphagia was reported in approximately 2% of all clinical trial patients. The benefits of Kybella treatment include minimally invasive, able to control placement and amount of submental fat reduction, skin tightening effect, and high efficacy [8]. The limits of Kybella treatment include 1 to 2 weeks of downtime following each treatment, multiple treatments required, possible exposure of platysmal bands, and high expense in relation to cost of multiple treatments [8].

Management

All reported cases of marginal mandibular nerve injury and dysphagia were temporary and resolved spontaneously [8,30,32]. The range of marginal mandibular nerve injury resolution was between 1 and 298 days, with a median of 44 days [30,32]. The range of dysphagia resolution was between 1 and 81 days, with a median of 3 days [30,32]. Patients experiencing either of the aforementioned complications should be reassured that all reported cases were temporary.

THERMAL MODALITIES (ULTRASOUND AND RADIOFREQUENCY)

The concept of high-intensity focused ultrasound has been around for more than 50 years and was initially developed to minimize the need for more invasive procedures when treating solid organ tumors, renal calculi, and uterine fibroids [35]. Currently, high-intensity focused ultrasound is used for nonsurgical fat reduction. High-intensity focused ultrasound works by generating high-energy (100–10,000 W/cm²) ultrasonic waves that converge at a targeted focal point, which then generate temperatures above a critical level in which adipocytes are unable to remain viable, and ultimately coagulative necrosis of adipocytes occurs [36]. There are various types of body contouring ultrasound devices on the market that are approved and not yet approved by the FDA. UltraShape (Syneron Candela, Wayland, MA, USA) and LipoSonix (Solta Medical [A division of Valeant Pharmaceuticals North America, LLC], Hayward, CA) are both FDA-approved ultrasound devices developed for body contouring.

Radiofrequency is an electromagnetic wave that generates heat in different tissues that was initially used for the treatment of facial rhytids and skin laxity [2,37]. Currently, radiofrequency is widely used for nonsurgical

fat reduction, skin tightening, and cellulite reduction [2,38]. Radiofrequency has the ability to deliver heat and increase deeper skin temperature without ablating the epidermis or dermis [2]. The heat is generated by orientation of electric dipoles, polarization of atoms and molecules, and displacement of electrons and ions in the tissue [2]. Both monopolar and bipolar radiofrequency devices are used with a frequency ranging between 3 kHz and 24 GHz [38]. The VelaSmooth (later improved and marketed as VelaShape) was the first FDA-approved radiofrequency device for body contouring [2]. Currently there are multiple radiofrequency modalities indicated for body contouring, such as BodyFX (InMode, Lake Forest, CA, USA), BTL Vanquish (BTL Industries, Marlborough, MA, USA), TruSculpt (Cutera, Brisbane, CA, USA), Thermage (Solta Medical [A division of Valeant Pharmaceuticals North America, LLC], Hayward, CA, USA), TriPollar (Pollogen Ltd. [A company of Lumenis], Yokneam, Israel), Accent (Advanced Beauty Cosmetics Ltd, Gravesend, Kent, United Kingdom), and Venus Legacy (Venus Concept, Toronto, Canada). As compared with high-intensity focused ultrasound there are less standardized treatment protocols with a wide range of treatment time and number and frequency of sessions because of varying devices.

Preprocedure Planning

Proper patient selection is necessary in patients seeking treatment with thermal modalities. Perform a skin pinch test to determine if there is a sufficient amount of fat to be treated. Skin laxity, former aesthetic procedures in treatment area, and any asymmetries should be considered and discussed with the patient before treatment to prevent an undesirable aesthetic outcome following treatment. In patients with skin laxity, radiofrequency devices may be more appropriate because they have skin-tightening capability. Obtaining baseline weight, circumferential measurements, and photographs should also be considered in preprocedure planning. As with all nonsurgical fat-reduction modalities, patients should understand that weight gain can contribute to an increase in subcutaneous fat and negatively impact treatment results. The treatment areas, times, and number of sessions required varies among patients and devices as does cost and should be discussed before treatment.

Patients should be prepared to anticipate common adverse effects following treatment with thermal modalities. The most common adverse effects following treatment with UltraShape include mild edema and folliculitis (if treatment area was shaved before treatment). The most common adverse effects following treatment with BodyFX include erythema and purpura,

which typically resolve within a few days [15,39]. It is also important to discuss the treatment and maintenance schedule. Unlike UltraShape, which typically requires a single treatment session and does not require maintenance treatments, BodyFX typically requires six to eight treatments sessions performed once per week and a maintenance treatment session is required once every 3 to 6 months [39,40]. Setting realistic expectations in regards to cost, number of treatment and maintenance sessions, outcomes, and limitations is essential to patient satisfaction.

Ultrasound (UltraShape)

Preparation and patient positioning

Remove all body jewelry and shave the treatment area if necessary before treatment. While the patient is standing use a caliper to confirm the subcutaneous fat thickness is greater than 1.5 cm in the treatment area then mark and measure the treatment area [40]. Gather the fat into a central treatment area using the UltraShape Reusable Strap Set. Patient should be positioned to ensure maximum fat thickness in the treatment area and a caliper should be used to confirm the subcutaneous fat thickness is greater than 2.5 cm in the treatment area in this position [40]. Place six tracking markers around the treatment area and adhere to either the patient's skin or clothing, but do not place on black clothing or background [40].

Procedural approach

Adjust the camera and zoom using the software so that the treatment area is centered and all of the markers are in the field of view then place the transducer on the treatment area surface and calibrate [40]. Ensure that the six tracking markers are identified and manually select the treatment area by touching at least eight points on the screen, then press the area button to close the area and enable the cross button [40]. Center the cross on the treatment area and place it so that it is aligned with the curvature of the body, then press the cross button to display treatment points and number of pulses for the treatment session [40]. Apply a generous amount of clear ultrasound gel over the entire treatment area, filling the umbilicus completely, and place the transducer on the treatment area moving in a circular motion to evenly distribute the ultrasound gel [40]. Maintaining good acoustic contact and not moving the transducer during energy delivery is essential for optimal treatment [40]. Move the transducer from one node to the next to deliver energy until completion of the treatment session (Video 3) [40].

Immediate post-procedural care

Immediately following the treatment, remove the tracking markers, ultrasound gel, and UltraShape Reusable Strap Set and clean the treatment area. Instruct patient that there are no restrictions and normal activities can be resumed.

Clinical results in the literature

There have been several clinical studies demonstrating the efficacy of high-intensity focused ultrasound (Table 5).

Radiofrequency (BodyFX)

Preparation and patient positioning

If medically permitted, patient should stop anticoagulants for 7 to 14 days before treatment to decrease risk of bruising [39]. Clean the treatment area with rubbing alcohol to remove any lotions or oils and to ensure the skin is clean and dry. Mark the treatment area while patient is standing and divide the treatment area into zones about the size of a large hand or four to eight footprints of the vacuum chamber of the handpiece [39]. Position the patient so that they are comfortable and that the treatment area is accessible. Select and set the appropriate treatment parameters according to skin type (sensitive, normal, or resistant) and the areas being treated.

Procedural approach

Place the handpiece onto the treatment area, maintaining full contact of the handpiece with the skin and applying slight pressure to enable maximum vacuum suction [15]. Press the footswitch to initiate radiofrequency current and suction, and heat the skin for the entire preselected pulse duration and then immediately move the handpiece to the adjacent tissue with an overlap of the vacuum chamber footprint of approximately 10% to 20% and initiate another pulse [15,39]. Continue multiple passes in this manner to maintain a temperature between 41°C and 43°C in the treatment zone for 5 minutes and then repeat the same process in the second treatment zone [15,39]. After treating the second treatment zone for 5 minutes, return to the first treatment zone and perform a second treatment pass of both treatment zones for a total time of 10 minutes in each treatment zone (Video 4) [15,39].

Immediate post-procedural care

The skin immediately following treatment will appear tight and erythematous. Clean the markings from the area and instruct the patient to moisturize the skin, and avoid scrubbing, scratching, very hot

TABLE 5
High-Intensity Focused Ultrasound Clinical Results

First Author, Year	Outcomes
Ascher [41], 2010	Abdominal circumference reduction of 2.47 cm, 3.51 cm, and 3.58 cm on days 14, 56, and 112, respectively, after 3 treatment sessions in 14-d intervals.
Chang et al [42], 2013	Mean circumference reduction of 3.91 ± 1.8 cm. MRI measurement of average fat thickness reduction was 21.4% and 25% on upper and lower abdomen, respectively.
Coleman et al [43], 2013	Average abdominal circumference reductions at midline, 2 cm above midline, and 2 cm below midline were 3.5 cm, 3.7 cm, and 3.0 cm, respectively. Reported adverse events were mild and transient in nature.
Fatemi & Kane [16], 2010	Waist circumference reduction of 4.4 cm at 12 wk post-treatment using a mean energy dose of 137 J/cm ² divided into 2 passes.
Jewell [3], 2011	Showed successful reduction of subcutaneous fat and no adverse effects were reported.
Jewell et al [19], 2012	Waist circumference reduction of more than 2 cm at 12 wk post-treatment at total doses of 141 J/cm ² (3 passes at 47 J/cm ²) and 177 J/cm ² (3 passes at 59 J/cm ²).
Moreno-Moraga et al [45], 2007	Mean reduction in fat thickness after 3 treatments was 2.28 ± 0.80 cm. Mean circumference reduction of 3.95 ± 1.99 cm. No adverse effects observed.
Niwa et al [46], 2010	Average reduction of 4.95, 4.88, and 3 cm in the circumference of the abdomen, hips, and thighs, respectively.
Shek et al [17], 2014	Waist circumference reduction of 2.1 cm at 12 wk post-treatment using a total energy dose of 150–165 J/cm ² .

(continued)

TABLE 5
(continued)

First Author, Year	Outcomes
Teitelbaum et al [4], 2007	Mean reduction of approximately 2 cm in circumference and 2.9 mm in skin fat thickness. Most effect achieved at 2 wk and sustained at 12 wk. Seven adverse events reported, all were mild and resolved within the study period.

Data from Refs. [3,4,16,17,19,41–46].

water, and direct heat exposure to the treatment area for 2 days [39].

Clinical results in the literature

There have been multiple clinical studies demonstrating the efficacy of radiofrequency in nonsurgical fat reduction (Table 6).

Rehabilitation and Recovery

There is typically no downtime and little to no restrictions with ultrasound and radiofrequency treatments. Therefore, normal activities can be resumed immediately post-treatment.

Potential Complications/Risks/Benefits/Limits

Ultrasound and radiofrequency are generally safe when performed properly. Typically, patients report only mild transient erythema, edema, discomfort, ecchymosis, and induration with ultrasound, which generally resolves within weeks after treatment [55–58]. However, more severe erythematous plaques have been reported [59]. Similarly, the most common adverse events caused by radiofrequency are temporary erythema, edema, purpura, and mild discomfort [15,39].

The benefits of ultrasound include safety and efficacy in reducing subcutaneous fat, noninvasive nature, no pain or discomfort during treatment session, single treatment required, no downtime, and minimal to no risk of complications. The limits of ultrasound include inability to tighten skin, cost of consumables, and indication only for abdomen.

The benefits of radiofrequency include safety and efficacy in decreasing subcutaneous fat, noninvasive nature, no downtime, ability to tighten skin, and minimal to no risk of complications. The limits of

TABLE 6
Radiofrequency Clinical Results

First Author, Year	Outcomes
Boisnic et al [15], 2014	Abdomen circumference reduction of 113.4–110.7 cm. Subcutaneous fat tissue thickness reduction of 40.5–38.5 mm. Adipose tissue weight reduction of 32.2–30.7 kg at 3-mo follow-up visit.
Duncan et al [47], 2016	1.1-cm reduction of abdominal region, 3 mo after the last treatment session using a protocol of 8 treatment sessions, 1 wk apart.
Duncan [48], 2017	Volumetric analysis and patient assessment showed similar results with a 2–3 “megasession” protocol when compared with 6–8 session traditional protocol.
Emilia del Pino et al [54], 2006	2.64- and 1.8-mm average reduction between the dermis and fascia in the thigh and buttocks, respectively.
Goldberg et al [49], 2008	2.45-cm decrease in thigh circumference after 6 sessions separated by 1 wk.
Manuskiatti et al [51], 2009	3.5- and 1.7-cm reduction of abdominal and thigh regions, respectively, 4 wk after the last treatment session using a protocol of 8 treatment sessions, 1 wk apart.
Sadick & Mulholland [50], 2004	4.14-cm reduction in thigh circumference after 16 treatment sessions, performed twice weekly for 8 wk.
Van der Lugt et al [52], 2009	Improvement of cellulite and body silhouette objectively detected at the final session, which slightly decreased at the 2-mo assessment. Histologic findings following the first session showed reactive edema and lysis of adipocyte membranes.

(continued)

radiofrequency include discomfort during treatment sessions, need for multiple treatment sessions, and cost of multiple treatment sessions.

TABLE 6
(continued)

First Author, Year	Outcomes
Wanithphakdeedecha & Manuskiatti [53], 2006	Average circumferential reductions of abdomen and thigh were 5.17 ± 1.04 cm and 3.50 ± 2.16 cm, respectively. Average circumferential reductions were sustained at 4-wk and 1-y follow-up visits. Average clinical improvement scores after the treatments series were 0.75 (approximately 25% improvement), and 1.75 (approximately 50% improvement), respectively.

Data from Refs. [15,47–54].

Management

Rare, more severe, complications from ultrasound and radiofrequency have been reported, such as burns, hyperpigmentation, and blisters. Local wound care is to be performed if burns or blisters arise [60,61]. Topical silver sulfadiazine or topical antibiotic ointment is the first-line treatment of burns and triple combination therapy consisting of topical hydroquinone, topical retinoids, and topical corticosteroids is the first-line therapy for hyperpigmentation [29,39,40].

SUMMARY/DISCUSSION

Patient demand for nonsurgical options for fat reduction and body contouring continues to steadily increase because many patients desire a safer alternative to liposuction. Cryolipolysis, chemical lipolysis, and thermal modalities, such as ultrasound and radiofrequency, are generally safe, well-tolerated, and effective modalities for nonsurgical fat reduction and have the potential to minimize complications and decrease downtime. These modalities vary greatly because some require a single treatment, whereas others require multiple treatment and maintenance sessions. Proper patient selection and thorough preprocedural patient assessments and documentation are critical to maximize patient outcomes. Providers need to be properly trained and provide appropriate counseling to patients. Although all the discussed nonsurgical fat-reduction modalities demonstrate efficacy and high patient satisfaction, outcome measures are variable and cannot be accurately compared. Future studies using

standardized outcome measures should be considered to accurately compare current nonsurgical fat-reduction modalities.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.yacs.2018.02.010>

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Nonsurgical Body Contouring



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KEYWORDS

• Nonsurgical • Body contouring • Noninvasive • Cryolipolysis • Radiofrequency • Laser

KEY POINTS

- Nonsurgical body contouring encompasses nonsurgical skin tightening, fat reduction, and cellulite treatments.
- Women and men are increasingly seeking nonsurgical body contouring procedures because of low downtime and high safety profiles.
- Current technologies use laser, radiofrequency, ultrasound, and cryolipolysis to achieve improvements in body contour.
- Cellulite treatments are minimally invasive procedures with growing popularity and success.
- Long-term studies demonstrating the durability of changes seen in nonsurgical body contouring are currently lacking.

INTRODUCTION

In 2016, there were more than 11.6 million nonsurgical cosmetic procedures performed in the United States, which included a 12% increase from 2015 in nonsurgical skin tightening procedures [1]. Nonsurgical fat reduction procedures have also seen similar increases in popularity. Men and women are both seeking options for improving their body contour with low downtime and high safety.

Body contouring allows for the treatment of isolated areas of adiposity or correction of asymmetries [2]. Commonly thought of the domain of liposuction, nonsurgical body contouring with new devices have emerged as an alternative to surgery. Together, nonsurgical skin-tightening and fat reduction procedures address the 2 components of body contouring, namely the outer skin and inner fat. Technologies include lasers, radiofrequency (RF), ultrasound, and cryolipolysis. Minimally invasive procedures combining these technologies with traditional

liposuction and other techniques for cellulite reduction also are considered a part of nonsurgical body contouring.

Nonsurgical body contouring is not a replacement for surgery in certain cases. Patients who have a severe skin excess or who are overweight are not ideal candidates for nonsurgical body contouring. Often these patients and those who experience massive weight loss require surgical procedures to achieve desired results and restoration of a more normal body contour.

SURGICAL TECHNIQUE

Preoperative Planning

Patients who often desire nonsurgical body contouring are unwilling to have surgical procedures performed either because of perceived downtime with surgery, medical contraindications, cost, or other motivations. The preoperative assessment should include a

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thorough history and physical examination with a specific focus on understanding patient motivations and expectations. This helps a provider assess whether a patient's expectations for correction are commensurate with expected results from the device(s) used. Patients should be evaluated for their height and weight, and a body mass index assessment should be made. Patients should be counseled that nonsurgical body contouring procedures are not weight loss procedures and that changes in weight will likely affect expected results. As with surgery, proper diet and exercise routines can help patients maintain results. Additionally, documented stable weight can be helpful in setting expectations of results.

Patients should be asked about prior nonsurgical procedures and their experiences. This can help a provider understand a patient's past expectations and level of satisfaction with obtained results. Providers can then tailor a plan of action based on these past experiences.

An assessment of skin quality is particularly important because many devices aim to stimulate secondary wound healing in the skin to achieve results. Younger patients with a stable weight are likely to have a different response than, for example, patients with a history of massive weight loss who have thin dermis.

Specific devices have manufacturer-issued contraindications, which should be reviewed by providers prior to performing the procedure.

Sample Device-Specific Contraindications

- CoolSculpting (Allergan, Dublin, Ireland)—cold-induced conditions, cryoglobulinemia, cold urticarial, paroxysmal cold hemoglobinuria, varicose veins, dermatitis, and cutaneous lesions
- Cellfina System (Merz North America, Raleigh, North Carolina)—coagulant disorders, diabetes, obesity, recent surgery, pregnancy, skin lesions, anticoagulation, untreated hypertension, vascular issues, and tumors
- Ultrashape (Syneron Candela, Irvine, California)—pregnancy, pacemaker, implanted cardiac defibrillator, abnormal fat metabolism, liver disease, connective tissue disorders, coagulopathies, wound healing issues, open wounds, fat thickness less than 1.5 cm or greater than 3 cm, hernias, keloids, or hypertrophic scars
- RF device—thin skin, autoimmune or collagen vascular disorders, smokers, patients on anti-inflammatory agents, pacemaker, or implantable device

Photographs are critical for documentation of the baseline appearance of the area to be treated. Post-procedure photographs at different time points can help visually track changes and can be useful for discussions with patients. Standardized photographs for the areas of interest should be obtained.

Patient Evaluation Should Include

- Focus on patient motivations and expectations
- Assessment of past nonsurgical procedures and patient's satisfaction
- Documentation of body mass index and stability of weight
- Assessment of skin quality
- Review device-specific contraindications for each technology type
- Preprocedure photography with standardized views

Preparation and Patient Positioning

Most nonsurgical body contouring treatments do not require a general anesthetic. Treatments like RF-assisted liposuction (RFAL) or certain cellulite treatments involve the use of tumescent solution that often contain local anesthetic.

Depending on the body site, the area should be cleaned thoroughly. If there is an invasive component to the treatment like RFAL or cellulite treatments, the area should be prepped and sterile techniques should be followed. Treatments that are purely external should adhere to clean technique.

Patients should be positioned such that they are comfortable during the period of treatment. If a patient is laying supine, adequate padding of pressure points and pillows below the knees can be helpful. Prone positioning patients also need to be padded appropriately.

Procedural Approach

In general, markings and photography are a critical part of body contouring and allow the provider to confirm with the patient the specific areas to be targeted with therapy. Each technology type has unique steps specific to the devices used. Representative procedural approaches have been provided.

BodyTite (Invasix, Yokneam, Israel)

- Access incisions made
- Infiltration of tumescence with reported ratios of 1:1, 2:1, and 3:1 (infiltration volume:aspiration volume)
- Skin lubrication with sterile gel to allow for RF penetration
- Administration of bipolar RF to desired depths of fat within tissue
- Standard mechanical or power-assisted liposuction for aspiration of fat until desired correction achieved
- Closure and dressings

CoolSculpting for Abdomen (Allergan, Dublin, Ireland)

- Identification of the peak of the bulge with marking using the planning template
- Insert gel trap along with contour and lock into the cooling cup
- Place adhesive pad over treatment area and engage vacuum to area of markings and begin treatment
- Once complete, remove vacuum and perform massage of treated area

Cellfina System (Merz North America, Raleigh, North Carolina)

- Infiltration of tumescence
- Use of vacuum handpiece in optimal orientation with activation of suction
- Identification of partial or complete release at desired depth of 6 mm or 10 mm using blade in guidance platform in targeted dimple
- Process continued until all desired areas of cellulite treated

Immediate Postprocedural Care

Depending on patients and physician comfort, preprocedure administration of pain medication or an anxiolytic can be helpful. Depending on the nature of the treatment, postprocedural pain and discomfort may require oral analgesics in keeping with a provider's preferences and patient's needs.

Massage is an adjunct often used in various types of nonsurgical body treatments like cryolipolysis. Compression garments can be of use in certain types of procedures to help maintain the achieved contour and also assist with patient comfort.

REHABILITATION AND RECOVERY

Nonsurgical body contouring procedures in general do not have major downtime. Depending on the extent and type of procedure, patients may have discomfort and some limitation in the resumption of all their normal daily activities, including exercise. Patients' expectations for postprocedural downtime and recovery should be discussed well in advance and tailored based on patient concerns and planned events.

CLINICAL RESULTS IN THE LITERATURE**Lasers**

SculpSure (Cynosure, Westford, Massachusetts) is a Food and Drug Administration (FDA)-approved 1060-nm laser for nonsurgical fat reduction. It has been used on-label for treatment of abdominal and flank fat reduction; 1060-nm lasers have minimal absorption in the skin with targets at the subcutaneous level. External laser application of the 1060-nm laser has been found to induce adipocyte injury by heating adipose tissues to 42°C to 47°C at a target depth of 1 cm to 3 cm. Treatment times last approximately 20 minutes to 25 minutes. Follow-up at 2 months, 3 months, and 6 months has found 14%, 18%, and 18% fat reduction, respectively, which was not found different in 1 study comparing it to cryolipolysis [3,4]. Longer-term follow-up studies are currently lacking.

Radiofrequency

External RF devices create an electrical field in the tissue being treated, which in turn causes molecular motion of charged particles and generates heat [5]. The current and contact time can be adjusted and alter the amount of heat generated in the tissue, which stimulates collagen contraction and wound healing with new collagen deposition and remodeling [6,7]. Devices using RF technology can be unipolar, monopolar, or multipolar and vary in the way the electric current passes between the device and tissue to either an electrode or a ground pad. In general, RF devices that use bipolar technology seem to require more treatments compared with monopolar RF [8].

The Thermage CPT device (Thermage, Hayward, California) is a monopolar RF device with different tip sizes for variable tissue targets. It has FDA approval for use in periorbital and full facial tissues and, more recently, body contouring with energy penetration up to 2 cm. Treatments take approximately 90 minutes for the body. It requires a grounding pad. Anolik and colleagues [9] looked at a series of 12 patients treated

with the device who had mild to moderate abdominal skin laxity and followed patients for 6 months. Patient satisfaction was highest at 2 months (89%) but trended downward at the 4-month and 6-month time points. Average decrease in waist circumference was greatest at 2 months at 1.7 cm⁹.

RF has also been used as an adjunct with liposuction. RFAL devices like BodyTite have an internal cannula tip that uses bipolar RF to generate heat, leading to liquefaction of adipocytes and shortening of collagen fibers and secondary neocollagenesis [10]. Because bipolar RF leads to more superficial healing, it may have more effect on the skin. The cannula tip can be used to target different layers of fat. This is followed with either mechanical or power-assisted liposuction. Several studies have looked at the BodyTite device for the treatment of abdomen, flank, thighs, and arms. Some series included those who had experienced massive weight loss. In general, patients experienced significant changes in weight and circumference with evidence of significant skin tightening regardless of anatomic location [10].

Ultrasound

Two major types of ultrasound energy devices exist: lower-energy microfocused ultrasound and high-intensity focused ultrasound. In general, lower ultrasound frequencies have deeper tissue penetration, whereas higher-frequency ultrasound has more superficial penetration [11]. Ultherapy (Ulthera, Mesa, Arizona) uses microfocused ultrasound to treat the superficial layers of the skin under the guidance of ultrasound imaging. It heats the underlying tissue to temperatures greater than 60°C with a depth of penetration of 5 mm, allowing the mid to deep reticular dermis to be treated [12]. It works by leading to focused coagulation and denaturation and contraction of collagen. Like other technologies, it also induces neocollagenesis. It has FDA clearance for use in the neck, chin, brow, and chest. Ultherapy has been used off-label in buttocks, arms, thighs, and knees [11,12]. A common complaint of treatment is pain or discomfort during the treatment, often ameliorated with topical anesthetics or oral pain medication. In the largest study of Ultherapy in the face with 93 patients, 58% showed improvement in skin laxity at 3 months [13]. Longer-term results were not presented. Ultrashape is used for lipolysis by using focused, pulsed ultrasound waves to selectively affect adipocytes and leave nearby structures undisturbed without generating heating. Multiple studies have demonstrated decreases in fat thickness with single and 3-treatment protocols [8].

In the authors' clinical experience, Ultherapy has worked well in the face and often has better results with a second treatment 6 months after an initial treatment. The first treatment can help create collagen in patients with thin, inelastic skin. The second round can then help tighten and lift with the collagen that has been laid down after the first treatment. Results in other parts of the body have been mild to modest at best.

Liposonix (Solta Medical, Hayward, California) uses high-intensity focused ultrasound to cause lipolysis. Multiple waves of ultrasound through the tissue leads to cavitation and shearing forces that in turn result in frictional heating [12]. The heat induces necrosis and apoptosis of adipocytes as well as neocollagenesis. Studies of Liposonix have noted adverse events like pain, swelling, and ecchymosis that self-resolved. Multiple studies have demonstrated reduction in waist circumference [12].

Cryolipolysis

Cryolipolysis devices take advantage of adipocyte susceptibility to cell death with cooling and induce adipocyte apoptosis and an inflammatory cascade that digests the dead adipocytes. Results can be seen by 4 weeks to 6 weeks once inflammation has been reduced and adipocyte volume has decreased [14].

The CoolSculpting device has FDA clearance for flank, abdominal, and thigh fat reduction. It has also been used to treat knees, arms, and gynecomastia off-label (Figs. 1 and 2). It draws tissue into the device using vacuum suction and then cools the underlying tissue for approximately 45 minutes. The treatment is followed by massage that helps improve the outcome with increased perfusion to the area. It is hypothesized that massage after treatment causes additional damage to susceptible adipocytes through tissue-reperfusion injury [15].

Multiple studies have demonstrated high levels of patient satisfaction with treatment to the abdomen, back, and flanks (73%) with statistically significant amount of fat loss [15]. Average reductions based on caliper and ultrasound measurement based on a review ranged from 14.7% to 28.5% and 10.3% to 25.5%, respectively. The most common complaint was delayed-onset pain at approximately 2 weeks postprocedure. A phenomenon known as paradoxical adipocyte hyperplasia (PAH), in which fat grows sometimes as a mass in the treated area, can occur sometimes as early as 2 months to 3 months postprocedure [15]. It is hypothesized that PAH could be due to recruitment and activation of stem cells or stimulation of a

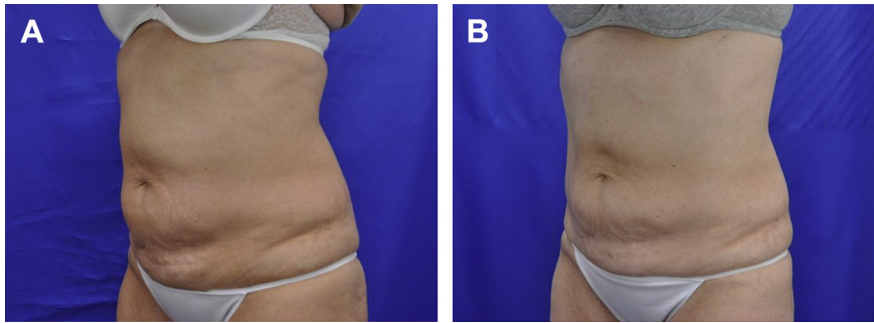


FIG. 1 A 42-year-old woman 3 months after cryolipolysis treatments (2 to the lower abdomen and 1 treatment to upper abdomen): (A) before and (B) after.

reparative processes to hypoxic adipocytes. To date, more than 291 patients have reported PAH in more than 2 million treatment cycles across the globe. Treatment recommendation is not more rounds of cryolipolysis but rather liposuction. PAH may be higher in patients of Hispanic descent and in men [16].

In the authors' clinical experience, cryolipolysis with CoolSculpting has been predictable and reliable in appropriately selected candidates. The authors have found patients with realistic expectations of a mild to moderate change in body contour the happiest users

of this technology. Additionally, those patients who want to minimize downtime, not have "surgery," or have contraindications to surgical procedures are also ideal candidates. Massage can be uncomfortable for patients but the authors believe it has led to better results, likely due to reperfusion injury. As more applicators come out, there are increasing areas of the body that are amenable to cryolipolysis. It is important to counsel patients that multiple cryolipolysis treatments may lead to a cost that is greater than a surgical procedure like traditional liposuction.



FIG. 2 A 50-year-old woman 3 months after 3 cryolipolysis treatments to the upper arms: (A) before and (B) after.

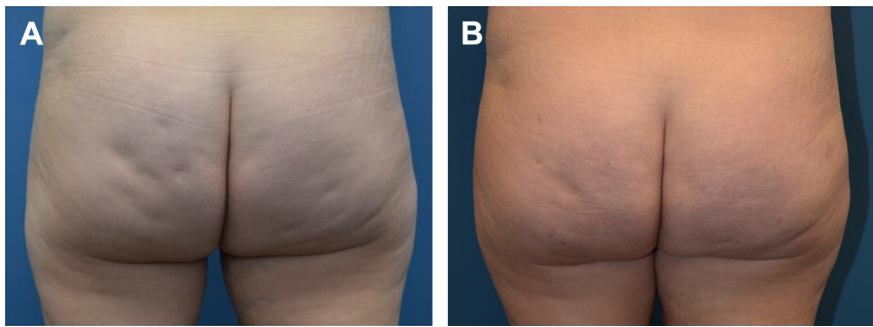


FIG. 3 A 36-year-old woman 6 month after single session of tissue stabilized-guided subcision for dimple cellulite of the buttocks: (A) before and (B) after.

Tissue Stabilized–Guided Subcision

Dimpled cellulite due to thick fibrous septae perpendicular to the skin can create irregular contours on the thighs or buttocks. Although this is typically not considered primarily due to fat, the tissue structure and presence of fibrous septae can lead patients to seek improvement in their body contour. Tissue stabilized–guided subcision with the Cellfina System is FDA approved for cellulite in the thighs and buttocks. Long-term studies with 3-year follow-up have demonstrated safety and durability of results using this system [17]. Photography and preoperative markings have been emphasized as critical components of ensuring adequate and complete correction of dimple cellulite (Fig. 3).

In the authors' clinical experience, Cellfina System has worked well for dimple cellulite after a single treatment. Patients' postprocedural pain often does not require narcotics. Patients have been satisfied and often have referred other friends and family for dimple cellulite correction. Appropriate patient selection is key for this procedure as with other nonsurgical body contouring.

POTENTIAL COMPLICATIONS, RISKS, BENEFITS AND LIMITS

A major limitation of the existing evidence on nonsurgical body contouring devices, regardless of technology type, remains that published studies have largely been industry sponsored. There are significant conflicts of interest between investigators and the few studies that are published.

Many procedures note temporary discomfort or pain but there are no documented long-term nerve injuries, dysesthesias, or chronic pain. In devices that combine energy and liposuction, inadequate removal of liquefied fat can lead to palpable fat nodules from fat

necrosis. Body contour irregularities can happen after any type of nonsurgical body contouring procedure. Temporary bruising or skin discoloration is not uncommon. Some energy devices have noted erythema, wheals, and edema after treatment [12].

Inadequate or uncorrected skin laxity remains a common complaint after nonsurgical or minimally invasive body contouring procedures [18].

Nonsurgical body contouring procedures can be used as an adjunct after body contouring surgery. It can be used for touch-up procedures or to enhance the final result after surgery.

MANAGEMENT

Individual nonsurgical body contouring plans should be tailored to the needs and expectations of the patient. Cost is also an important factor that should be discussed with the patient. Some patients who are unwilling or unable to undergo surgical procedures may find the cost and number of treatments needed to achieve a desired effect prohibitive.

SUMMARY

Nonsurgical body contouring aimed at skin tightening, fat reduction, and improvement in contours by treating diseases processes like cellulite are growing in popularity. Men and women are seeking ways to achieve improvements in body contouring with minimal downtime and the stigma of "surgery." Patient selection and education are perhaps the 2 most important and critical steps in obtaining reasonable results for patients. Long-term durability of results and cost-effectiveness versus surgical body contouring remain unknown at this time.

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Nonsurgical Vaginal Rejuvenation



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KEYWORDS

- Vaginal rejuvenation
- Vaginal relaxation syndrome
- Genitourinary syndrome of menopause
- Vulvovaginal atrophy
- Laser
- Radiofrequency
- Urinary incontinence

KEY POINTS

- In the past 5 to 10 years, a surge of interest in female intimate wellness, specifically vaginal rejuvenation, both surgical and nonsurgical, has been witnessed.
- For both cosmetic and functional reasons, increasing numbers of women have sought alternatives to traditional therapies for dealing with the common but unwelcome changes that occur to the vaginal and vulvar tissues induced by maternity, weight fluctuation, hormonal change (sometimes following cancer care), natural aging, and menopause.
- Traditional nonsurgical options of improving vaginal well-being for the premenopausal as well as postmenopausal woman have proven to have limited long-term benefit, and therefore, patient compliance with these methods can be poor.
- Not only do many of the conditions and symptoms of vaginal relaxation syndrome and genitourinary syndrome of menopause and its associated symptoms of vulvovaginal atrophy affect female intimate wellness over time, affecting quality of life, self-esteem, and the quality of interpersonal relationships, but also these conditions, if left untreated, tend to worsen with age.
- In order to offer patients the most effective and up-to-date therapies, the treatment approach should be individualized, and each practitioner should have a thorough breadth of knowledge regarding the cause of the conditions patients present with as well as a thorough understanding of technology that now exists to treat these issues.

Nearly 5 decades ago, gynecologists and plastic surgeons pioneered the integration of lasers for the ablation of diseased tissue by vaporization, ablation, and tissue contraction [1,2]. Since then, a host of energy-based devices have emerged to treat pelvic pathologic condition, improve fertility, and rejuvenate skin of the face and body. Current fractional (carbon dioxide [CO₂] and erbium:YAG) and hybrid laser-based technologies, nonablative and resurfacing radiofrequency (RF) technologies, and even a novel electromagnetic therapy device may now be used to treat patients dealing with genitourinary syndrome of menopause or vulvovaginal atrophy (GSM/VVA) and

vaginal relaxation syndrome (VRS) symptoms as well as their frequently associated symptom complexes of sexual dysfunction, urinary incontinence (UI), and even true skin disorders, such as lichen sclerosis.

INTRODUCTION

The American Society for Aesthetic Plastic Surgery procedural statistics reported an increase of 23% in surgical labiaplasty procedures performed in 2016 by its members compared with 2015 (the first year for which such statistics were available). Thirty-five percent of plastic surgeons now perform surgical labiaplasty, and they

Disclosure: J.B. Samuels is a speaker and consultant for the following device manufacturers: InMode, BTL, and Syneron-Candela, and receives speaking honoraria for the same.

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performed more than 10,000 labiaplasty procedures last year [3]. This number does not include the number of surgical labiaplasties performed by gynecologists. Along with this newer area of surgical interest, there has also been a rapid growth in the number of treatment options for nonsurgical vaginal rejuvenation. Accordingly, more than half a million nonsurgical feminine rejuvenation procedures were performed in 2016, generating \$500 million in incremental fees for practitioners [4]. It is thus very important to catalog the most current and effective advances in this rapidly growing field of care of the female patient, so that treatment indications and efficacy remain at the forefront of procedures offered to patients by a variety of practitioners.

PATHOPHYSIOLOGY

GSM or VVA represents a constellation of symptoms [5] that, although underreported, has been estimated to affect up to 50% of postmenopausal women [6] and affects quality of life [7,8] as a result of the natural decrease of estrogen levels after the onset of menopause (naturally or iatrogenic). Before menopause, with normal circulating levels of endogenous estrogen, vaginal canal physiology is characterized by the

presence of a thickened, rugated, nonkeratinized epithelial layer that is well vascularized and self-lubricated. As estrogen levels decline (or are deprived as in some patients with hormonally treated malignant conditions), the vaginal wall loses collagen and elastin and becomes thinner, there is a reduction in blood flow, and there is a changed quality and quantity of vaginal secretions. The epithelial surface becomes pale with loss of rugation, more friable with petechiae, and irritation and bleeding may occur after minimal trauma. There is a decrease in the normal epithelial cell metabolism due to loss of normal blood flow and decreased nutritive vaginal transudate, glycogen stores of healthy epithelial cells falls, leading to a reduction in the amount of protective lactobacilli content, which need glycogen to thrive. The latter leads to an increase in the normally acidic pH to a more alkaline state, and some of the protective function of the vaginal wall is lost, allowing the increased susceptibility to trauma, infection, vaginitis, lower urinary infections, and urogenital pain (Fig. 1) [5,9–11].

CLINICAL TREATMENT INDICATIONS

The symptoms of GSM/VVA commonly include, but are not limited to, reductions in the diameter and elasticity

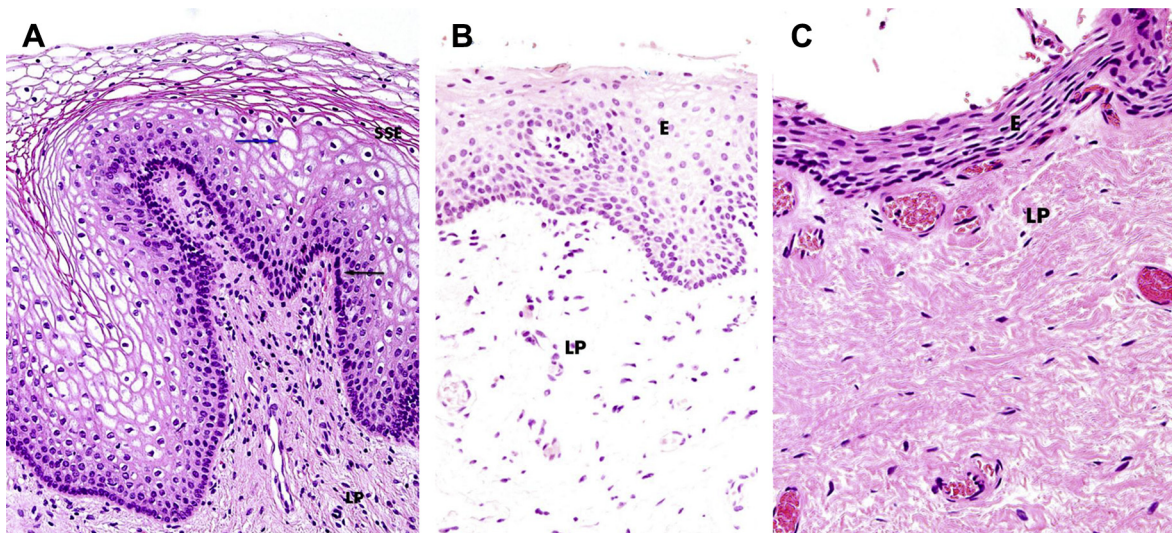


FIG. 1 Histologic sections of the vaginal wall. (A) Normal. (B) Moderately atrophic. (C) Severely atrophic. (A) Estrogenized vaginal histology. The 2 upper layers of the vaginal wall are shown: stratified, squamous epithelium (SSE) and the lamina propria (LP). The stratified squamous epithelium is rich in glycogen (larger cells with abundant clear cytoplasm—blue arrow) and is nonkeratinizing. The basal cell layer (black arrow) consists of a single layer of columnar cells. (B) Moderately atrophied vagina: atrophy is shown by thinner epithelium (E) and loss of maturation (smaller cell size with less cytoplasm) on the surface. (C) Marked vaginal atrophy. (hematoxylin and eosin stain and $\times 40$ magnification). (Courtesy of Ahinoam Lev-Sagie, MD, Hadassah-Hebrew University Medical Center Jerusalem, Israel; with permission.)

of the introitus and internal vaginal canal, thinning of vaginal tissues, and loss of natural lubrication, which often leads to the secondary effects of dryness, itching, irritation, dyspareunia, sexual dysfunction, and dysuria. Stretching and trauma to the vaginal tissues from normal aging, maternity, and childbirth can cause not only functional changes of lack of support to the vagina, urethral mechanism, and pelvic floor, leading to pelvic organ prolapse, rectal or vaginal prolapse, UI, and decreased sensation during coitus [12] to varying degrees, but may also lead to cosmetic concern in many women due to the aged appearance of the vulvovaginal structures over time. The symptoms of VRS can therefore affect premenopausal as well as postmenopausal women and cause many to express both functional and cosmetic concerns. Many complain about the excessively redundant labia minora and clitoral hood areas, asymmetrical labia minora tissue, visible fullness of the labial tissues when viewed naked or in tight clothing, chafing and irritation during exercise (running, biking, horseback riding) or intercourse, and embarrassing periods of audible “vaginal gas.” Another common cosmetic concern is the atrophy, deflated appearance, or hyperpigmentation of the labia majora.

TRADITIONAL TREATMENTS MODALITIES

Traditional nonsurgical methods targeted to the vaginal tissues themselves for functional improvement of symptomatic GSM/VVA/VRS include nonhormonal vaginal lubricants, continued sexual activity, and local and systemic estrogen, or estrogen modulator (Ospe-mifene) therapy. Traditional nonsurgical methods of treating symptoms resulting from the laxity and loss of support of the deeper vaginal tissues include Kegel exercises, bladder training, overactive bladder medications, and the wearing of pessaries or urinary pads [9]. However, because of mixed results, complications of topical estrogen products (uterine bleeding, breast pain, and perineal pain), and poor compliance with many of these measures, many patients in the past have turned to surgical procedures such as vaginoplasty, complex pelvic floor reconstruction, or bladder suspension surgery. Advantages of the newer nonsurgical energy-based treatment modalities are that they do not possess the potential morbidity of the surgical procedures, they favorably affect vascularization on all levels of the vaginal, periurethral, and pelvic floor connective tissue layers (as opposed to the superficial epithelial benefits of estrogen therapy), and their effect appears to have long-lasting benefits (again, as opposed to the dissipation of benefit if estrogen use

is discontinued) [13–15]. In addition, many women express concern over hormonal therapies due to cancer-related consequences. Finally, unlike skin complications, such as hypertrophic scarring, unwanted tissue contraction (ectropion), pigmentary change, burns, or disseminated infection, which have all been reported after fractional laser skin resurfacing of the face, neck, or body [16], no major complications have been reported after energy-based vaginal rejuvenation procedures [15].

CURRENT ALTERNATIVE NONSURGICAL VAGINAL REJUVENATION OPTIONS

Among the new nonsurgical modalities being offered to female rejuvenation patients are lasers and RF devices, which target the vaginal connective tissues, and the newest device, which uses electromagnetic therapy that targets muscle.

Lasers, or “light amplification by stimulated emission of radiation,” employ wavelengths that are selected in order to target a specific tissue chromophore, such as water in the vaginal tissues [17]. Selective photothermolysis describes the desirable clinical effect of selectively absorbed laser wavelengths by a specific chromophore in the target tissue [18]. In addition, the laser pulse duration can be controlled to confine the thermal damage to the target area, ideally delivering a pulse of light whose duration is less than or equal to the thermal relaxation time (or time for the temperature to decrease by 50% from the temperature immediately after laser exposure) [19]. Furthermore, using fractional beam technology, microthermal zones of tissue injury occur separated by intervening nests of uninjured skin, the effect of which is to hasten recovery and reduce the incidence of adverse events [20,21]. The most commonly used lasers for vaginal rejuvenation are fractional CO₂ and erbium:YAG.

RF devices use electrical conductance, in the form of rapidly alternating electrical current, to cause oscillation of cellular structures that are in the electrical path, thereby increasing intermolecular motion. As the current flows alternatively, molecular collisions increase, thereby creating thermal energy (heat). Thus, RF technology uses the impedance (resistance) of tissue to generate heat rather than directly transferring heat, and energy is dispersed to the bulk of the 3-dimensional tissue as a whole, although at controlled depths. The configuration of electrodes in RF devices can be monopolar, bipolar, or tripolar, and beyond, all of which have been used for cutaneous applications. Historically, most RF vaginal devices were monopolar

devices; however, these initial devices could have relatively limited efficacy because of pain, burns, or other adverse effects [22,23]. More recently, bipolar RF devices, incorporating both positive and negative electrodes, have been developed with potentially greater efficacy and an improved safety profile because of the creation of a closed electrical circuit, which makes it easier to control depth of penetration and to potentially target some tissues while sparing others [24,25]. Technical parameters of the various devices discussed are listed in Table 1.

LASER-TISSUE INTERACTIONS: ABLATIVE LASERS

Carbon Dioxide Laser

The CO₂ laser emits light at a wavelength of 10,600 nm, which is strongly absorbed by tissue water [18]. With fractional CO₂ devices, an array of microbeams of laser light is delivered to create microscopic columns of energy-mediated effects using either optical scanners

to deliver the spot or a stamping technique [20]. The microscopic lesions extend from the vaginal epithelium into the lamina propria, to depths dictated by laser energy density and spot size. The evolution of this technology has largely been responsible for the conversion of these energy-based devices from cutting and coagulating tools to true cell activation and tissue rejuvenation tools. Lessons learned from the effects of these lasers on skin have been instrumental in the understanding of how they can be used to rejuvenate the vaginal mucosa to treat patients with GSM/VVA/VRS [15]. The mechanism of action of fractional CO₂ occurs via delivery of a supraphysiologic heat energy that causes a rapid thermomechanical tissue destruction (ablation) that is surrounded by a peripheral zone of coagulation that causes tissue tightening through the process of heat-induced collagen shrinkage and neocollagenesis. These desired collagen changes occurs at temperatures between 45°C and 50°C in the zone surrounding the ablated tissue [26,27]. The level of supraphysiologic heat generated by the CO₂ laser induces a rapid and transient heat-shock response that

TABLE 1
Technical Parameters of Vaginal Probes and Device Specifications

Brand Name, Technology	Laser Type/ Wavelength (nm) or RF	Pulse Duration	Maximum Energy/ Pulse	Surface Area “Lased”/“Heated” Exposure
Laser				
Alma lasers	CO ₂ , 10,600	400 ms	500 mJ (per pixel)	10 mm ²
Fotona	Er:YAG, 2940	250 ms	240 J (per pass) 3 J/cm ²	80 (cm ²), nonablative, entire surface
Focus Medical	CO ₂ , 10,600	1–200 ms	60 mJ	10 mm ²
Lumenis	CO ₂ , 10,600	NA	7.5/10/12.5 mJ	NA
Lutronic	Er:YAG,– 2940	NA	NA	NA
Sciton	Hybrid: 2940/1470	150/20 ms	300/100 mJ	1.5–2.5 mm ²
Syneron-Candela	CO ₂ , 10,600	20–1066 ms	70 mJ	10 mm ²
RF				
ThermiVa	* <i>Monopolar</i> RF 460 KHz	Continuous	20 W/operator adjustable up to 47°C	10 mm ²
Ultra Femme 360 procedure by BTL Exilis Ultra 360	<i>Monopolar</i> RF 3.25 MHz	Continuous	90 W/operator adjustable up to 43°C	235 mm ²
VOTIVA by INMODE (Forma V)	<i>Bipolar</i> RF 1 MHz	Single-pulse continuous repeat	40–65 W/operator adjustable up to 43°C (real time)	50 mm ²

Abbreviation: NA, not available.

temporarily alters cellular metabolism and activates a small family of “heat-shock proteins” (HSPs). HSP70, which is overexpressed after laser treatment, stimulates transforming growth factor- β , triggering an inflammatory response that stimulates fibroblasts, which produce new collagen and extracellular matrix. The laser’s emissions characteristics specifically target the energy load to the mucosa while avoiding excessive localized damage. This aspect of its design allows for restoration of the permeability of the connective tissue, enabling the physiologic transfer of various nutrients from capillaries to tissues. Several clinical trials and published reports now provide consensus opinion regarding the beneficial and restorative effects of fractional CO₂ treatments upon vaginal tissue histology; however, these studies typically followed patients for only 3 to 6 months after the last of 3 treatments performed at monthly intervals [15,28,29]. A recent study reported that the 1-year outcome of average Vaginal Health Index remained statistically significant after CO₂ laser treatment [30]. Another prospective institutional review board–approved study, performed at 2 clinical sites in the United States by urogynecology and plastic surgery (this author), presented 1-year outcomes and histologic validation of clinically significant improvement in GSM/VVA symptoms for up to 12 months after laser treatment in 100% of 40 postmenopausal patients [31]. Fig. 2 from this study depicts histologic findings at 8 months after baseline (6-month follow-up).

The posttreatment epithelium is thicker with a better degree of surface maturation, and there are an improved vascularity and water content, reduced inflammatory cell infiltrate, and increased collagen and elastin content. Clinical findings from multiple CO₂ published reports

in peer-reviewed publications have shown subjective improvement in self-reported sexual function, vaginal tightness, mild to moderate UI, and decreased severity of vaginal pain, burning, itching, dryness, dyspareunia, and dysuria associated with GSM/VVA [30–33].

Erbium:YAG Laser

The Er:YAG laser is a near-infrared ablative laser that emits light at a wavelength of 2940 nm, which is close to the absorption peak of water and yields an absorption coefficient that is actually 16 times higher than that of the CO₂ laser; however, the depth of penetration of Er:YAG compared with CO₂ is more superficial and has less associated thermal effect in surrounding tissue, so that the Er:YAG laser is a true ablative laser pulse [18]. An Er:YAG laser that delivers wavelengths of 2940 nm and 1470 nm to deliver both an ablative and a nonablative pulse is also available. Fractional Er:YAG laser treatment of vaginal mucosa has been shown to create increased thickness and cellularity of the epithelium and a more compact lamina propria with a denser arrangement of connective tissue. Increases in collagen and elastin content were also demonstrated with short-term 2-month follow-up [34].

Radiofrequency

RF energy is dispersed in a 3-dimensional, bulk tissue heating manner, albeit at controlled depths, rather than using the selective photothermolysis mechanism of action used by laser technology. In RF-tissue interactions, heat generated in the dermis reaches a thermal dose threshold, above which collagen begins to denature (~60°C) and to fully denature (70–75°C) [21]. Partial denaturation of collagen by RF is maximal at

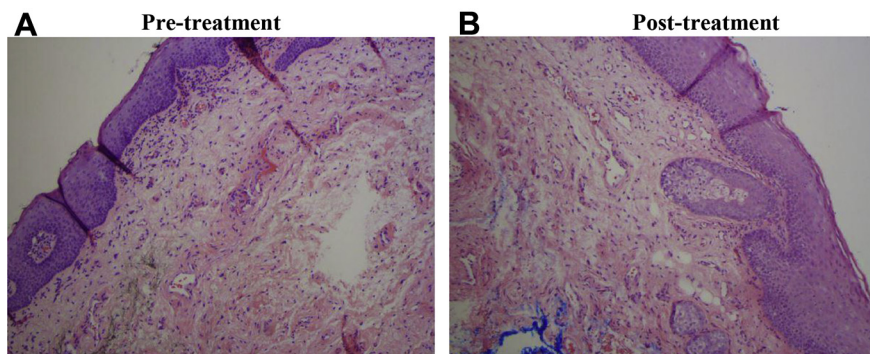


FIG. 2 (A) Pretreatment histology of a 71-year-old woman. (B) At 5 months after baseline, histology showed increased collagen and elastin staining as well as a thicker epithelium with an increased number of cell layers and a better degree of surface maturation. (hematoxylin and eosin stain and $\times 40$ magnification). (Courtesy of Julene B. Samuels, Louisville, KY and Martin Garcia, Jacksonville, FL; with permission.)

67°C, and this correlates with optimal neocollagenesis, neoelastogenesis, and clinical effects in the skin. Temperatures at 40°C to 45°C induce production of collagen by fibroblasts and are effective in skin tightening [35]. However, surface temperatures of the skin exceeding 45°C have been correlated with pain and thermal burns during and after RF treatment.

Current monopolar RF devices for vaginal treatment use “mobile RF delivery,” whereby afferent cutaneous pain nerves are cooled to avoid a surface temperature exceeding the trigger threshold of 45°C, whereas heat accumulates in the target collagen and dermal structures [36]. A newer noninvasive bipolar RF device developed for vaginal rejuvenation offers technology that allows for prolonged, controlled dermal heating while limiting the potential for side effects. Because of the configuration of the positive and negative electrodes within the hand piece, the depth of the RF current is carefully controlled to create uniform dermal heating. The device also allows the setting of the optimal dermal temperatures to be maintained throughout the treatment as well as the energy delivered. There are sensors incorporated to monitor real-time impedance, contact, and temperature, with automatically controlled cutoff and reactivation mechanisms designed to maintain the preset parameters throughout the treatment [37]. The manufacturer also offers with the device a bipolar fractional RF hand piece for quick resurfacing of the external vulvar and labial tissues if cosmetic improvement (tightening, textural improvement, and correction of hyperpigmentation) is desired.

When compared with the many beneficial effects of laser tissue interaction, RF appears to provide similar applicability for vaginal rejuvenation with reports in the literature of the creation of new dermal volume, and improvement in skin laxity and elasticity [38]. In addition, when dermal collagen is heated to a certain temperature (by any energy method), the partially denatured collagen serves as a signal for neocollagenesis [35]. RF has also been shown to induce neoelastogenesis and vaginal tightening, especially helpful in cases of VRS [38].

Other points of comparisons to be made between laser and RF technologies include the following considerations:

- Device acquisition cost (advantage RF)
- Maintenance contracts (advantage RF)
- Shorter treatment time (advantage laser and bipolar RF)
- Environmental biohazard, that is, laser plume (advantage RF)
- Ability to treat external lesions (advantage excisional options on laser)

- Ability to treat external vulvar tone, texture, and hyperpigmentation (advantage laser and bipolar RF microneedling, because hyperpigmentation correction requires ablative capacity)

The widths of the vaginal laser probes on devices summarized in this review vary between 19 and 38 mm, and the RF probes are 15 to 25 mm. These probe widths are easily and comfortably accommodated by premenopausal and postmenopausal patients.

BEYOND THE VAGINA: ADDITIONAL APPLICATIONS

Urinary Incontinence

There are 4 main types of UI, the involuntary leakage of urine:

- Urge incontinence due to an overactive bladder
- Stress incontinence due to poor closure of the bladder
- Overflow incontinence due to either poor bladder contraction or blockage of the urethra
- Functional incontinence due to medications or health problems making it difficult to reach the bathroom

Stress urinary incontinence (SUI) is the most common variety, and it is also the most amenable to improvement with nonsurgical vaginal rejuvenation devices. SUI usually results from weakening of the support naturally provided to the bladder, urethra, and pelvic floor by normal healthy collagen and elastic connective tissue because these tissues age or undergo changes with various pathologic conditions [39]. Urethral support, anterior vaginal wall tightening, and even pelvic floor support can be improved by exploiting the energy-induced tightening effect of these devices. Published reports cited previously in this review confirm enhanced urinary control after treatment of SUI with CO₂ laser, Er:YAG laser, and RF, all of which trigger a photothermal effect, as deep as 0.5 mm inside the vaginal wall, resulting in reductions in tissue volume via collagen and connective tissue shrinkage via HSP effects. The mechanical pull induced by the photothermally affected superficial tissue layers is presumed to exert a pull on the deeper tissue layers such that a globally beneficial tightening effect occurs, while at the same time, thermally induced neocollagenesis improves thickness, elasticity, and firmness of the vaginal wall [40,41].

Although all of the energy-based devices discussed here have application and proven clinical efficacy for improving SUI, there are a few devices with special adaptation for the treatment of SUI worthy of

mention. Er:YAG laser treatment is available with a special accessory Incontilase kit that offers separate hand pieces, adaptors, and a laser speculum for ease of full spot, fractional, or patterned spot energy delivery to the anterior vaginal wall and periurethral tissues [41,42].

Another new technology to arrive to treat all types of UI is high-intensity focused electromagnetic technology (HIFEM). A noninvasive magnetic field triggers intense pelvic floor muscle contractions by targeting neuromuscular tissue and inducing electric currents. These electric currents depolarize neurons resulting in concentric contractions that are much higher than what can be achieved through voluntary physiologic muscle contraction (eg, Kegel exercises). These contractions, pulsed and comfortably held for several seconds, are created independently of brain function and target directly the peripheral nerves in the pelvic floor. A single session of HIFEM brings thousands of supramaximal pelvic floor muscle contractions, important in muscle reeducation in incontinent patients. Preliminary results show a high response rate (>90%) after 6 total treatments, performed twice weekly, in 60 patients with all types of UI (Fig. 3) (Berenholz J, Sims T, Botros G. HIFEM technology (EMSELLA by BTL)—a new perspective

in addressing stress urinary incontinence. Personal communication [2017]).

Lichen Sclerosus

Lichen sclerosus is a benign, inflammatory skin disease of unknown cause that, when affecting genital tissues, may result in vulvar scarring, loss of portions or all of the labia minora due to resorption, clitoral adhesion, and narrowing of the introitus. The disease is progressive, and symptoms include pruritis, soreness, irritation, pain, dysuria, dyspareunia, and sometimes perianal involvement. Treatment traditionally involves topical corticosteroids (clobetasol propionate) [43]. Recently, several reports of successful treatment with fractional CO₂ laser technology have emerged that in many cases lead to not only symptom resolution and curative histologic change but also visible improvement of skin color, elasticity, and vascularity [15]. Clinical trials are ongoing in the use of fractional lasers in the treatment of lichen sclerosus.

Female Genital Aesthetics and Intimacy

The aesthetics of the female genitalia have become an area of particular concern among women over the past decade, possibly facilitated by the popularity of Brazilian waxing, fashion trends, and media promotion of nude



FIG. 3 EMSELLA by BTL. High-intensity focused electromagnetic technology. (Courtesy of BTL Industries, Inc, Marlborough, MA; with permission.)

images. In addition to the many functional reasons women seek corrective surgical and nonsurgical options to deal with GSM, VVA, and VRS, there is evidence that the increasing request for vaginal and genital rejuvenation procedures may in fact also derive from women's desire for an improved vulvar aesthetic. The current trend appears to be toward a more minimalistic appearance of the external genitalia: narrowed, minimally visible and symmetric labia minora as well as tighter and "brighter" labia majora that are smooth, tight, nonpigmented, and full. The beauty ideal that seems to be emerging is therefore that of a "clean slit" characterized by a vulvar area that seems to end in a perfect point of nothingness [44]. Prolific use of the Internet and exposure to images of modified vulvas may well influence women's perceptions of what is normal and desirable [45]. Associations have been made between women's satisfaction with anatomy of the genitalia and quality of life and sexual satisfaction, so that demand is on the increase for procedures relating to improving form and function of the female genitalia. It is therefore very important for practitioners in the field to be as knowledgeable regarding treatment indications and alternatives as they are facile in selecting and performing the nonsurgical treatment options of choice.

SUMMARY

The plethora of data being generated from the large number of publications in peer-reviewed journals on cell activation and vaginal wall rejuvenation after the use of light and energy-based devices is encouraging. There seems to be firm consensus that these devices are indeed effective in treating GSM-related symptoms, rejuvenating intimate female anatomy, and restoring a sense of female intimate wellness for many women after childbirth and menopause. The currently available data on the effects of fractional laser and RF devices support a rejuvenation effect on vaginal tissues that results from the following unequivocal histologic changes: thickening of glycogen-enriched postmenopausal epithelium, neovascularization, and neocollagenesis in the lamina propria, increased lactobacilli population, reduced pH, vaginal wall tightening, improved urination control, tightening and brightening of the external vulvar and labial skin, and improved urinary control, and all with minimal risk of short-term or long-term complications [15]. The choice of which device to incorporate into an individual practitioner's practice remains a challenge to all providers in this space. Manufacturers likewise need to continue to enhance and improve ease of operability of their individual patented technologies

to try to address the many and varied needs of patients and providers alike.

Controversial issues that remain to be elucidated include the following:

- The determination of which light and energy-based devices provide the most thorough and long-lasting improvements of GSM, VVA, and VRS symptoms, and therefore, which devices offer the longest re-treatment intervals (studies supported by histopathological data comparing the *degree* of induced neocollagenesis, neocollagenesis, and cellular change as well as nervous tissue changes of laser and RF)
- Age group-specific device usage advantages (are laser or RF more, or equally, effective in different age groups of women, ie, the premenopausal or postpartum woman vs the postmenopausal woman)
- Which devices provide the most cost-effective modality of treatment, given that this analysis includes a consideration of the cost of device acquisition, disposables, and maintenance, as well as a consideration of environmental hazard (laser plume), necessary staffing for device operation, space considerations, or multimodal use indications that benefit a practice
- The further study of the pathophysiology and optimal device treatment of chronic, progressive conditions, such as lichen sclerosis (estimated to affect up to 1 in 59 patients in a general gynecologic practice [43]).
- The potential of the additive effect (if any) upon the use of light and energy-based devices with platelet-rich plasma/growth factor, hyaluronic acid, and estrogen-priming therapies
- Optimization of treatment options and protocols for the treatment of SUI
- Comparative analysis of the cost-effectiveness of light and energy-based treatment options with other interventions
- Further elucidation of any unwanted long-term sequelae
- US Food and Drug Administration approval for use of these devices in sexual function and GSM/VVA (at the time of this writing, only InMode Votiva FormaV has on-label indication)

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Cosmetic Surgery Following Weight Loss Surgery



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KEYWORDS

- Body contouring • Massive weight loss • Postbariatric • Brachioplasty • Thighplasty • Mastopexy • Abdominoplasty

KEY POINTS

- Massive weight loss patients require comprehensive preoperative evaluation and management of expectations.
- Patients and surgeon must together develop a plan and schedule for the order and timing of each surgical procedure, based on the patients' priorities.
- Procedures are wide ranging and include contouring of the abdomen, inner and outer thighs, buttocks, back, breasts, arms, and face/neck.
- Staging procedures are often required to avoid simultaneous opposite directions of pull.
- Complications are common after cosmetic procedures for massive weight loss but are often minor in severity and easily managed in the office.

INTRODUCTION: NATURE OF THE PROBLEM

The obesity epidemic continues to increase worldwide, despite continuous efforts to battle weight gain (Figs. 1–9). Current treatment options include diet and exercise, medical weight loss, and bariatric procedures. As more patients turn to surgical management of obesity, an increasing number of patients present for body contouring procedures after massive weight loss (MWL), most of which are considered cosmetic procedures by insurance carriers. Although abdominoplasty and breast lift surgery are the most common, brachioplasty and thighplasty for excess extremity skin are gaining in popularity, as are lower body lift (LBL)

procedures. Deformities after weight loss are often severe and unpredictable, sometimes causing significant functional impairment due to rashes or poor-fitting clothes. Attention to preoperative assessment, surgical planning, and postoperative management is critical to optimizing results for this complex patient population.

SURGICAL TECHNIQUE Preoperative Planning

Careful assessment of any patient who presents for body contouring after MWL, defined as a loss of greater than 50% of excess weight more than the ideal body

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FIG. 1 Markings for a brachioplasty.

weight [1], is paramount to performing surgery safely and minimizing complications. It cannot be overstressed that a focused history and physical will keep a surgeon—and patients—out of trouble. The surgeon should understand the patients' reasons for pursuing surgery as well as their expectations for eventual results. The latter must be reasonable and aligned with what the surgeon can offer.

Given that these operations are superficial, involving mainly skin and subcutaneous structures, they are considered low risk by the American College of Cardiology and American Heart Association [2]. Suitability for general anesthesia should be obtained from a preanesthesia unit, if one is available, or from the patients' primary care physician or other medical specialist. For patients with a positive psychiatric history, or if there is a concern about psychiatric stability or body dysmorphic disorder, a referral to a mental health specialist is recommended. Patients on chronic pain medication should be sent back to the physician managing their pain medications, and a clear plan should be developed for postoperative pain control.

Modifiable risk factors include medical comorbidities, body mass index (BMI), tobacco use, and nutrition status; these should be optimized before agreeing to surgery. Management of medical

comorbidities, such as hypertension and diabetes, should be left to a primary care physician or generalist. All patients should be evaluated equally, as BMI cutoffs may not consider significant deformities of certain areas. After weight loss, patients should have a stable weight for at least 3 months, within a 5-kg range [3]; this generally occurs approximately 15 months after bariatric surgery. Nutritional assessment should include, at a minimum, screening of albumin; vitamins A, B, D, E, and K; and iron levels, especially in patients who have had malabsorptive bariatric procedures, such as Roux-en-Y gastric bypass or biliopancreatic diversion. Studies have shown that, despite supplementation, up to 50% of patients who have had bariatric surgery have at least one elemental or nutritional deficiency [4,5]. A complete blood count should be obtained on all patients who have sustained MWL. A fast and easy set of questions that can be asked in the clinic is included in Box 1.

Although previous events in a patient's history, such as a cardiac or cerebral ischemic event, cannot be modified, perioperative risks can be reduced by following accepted guidelines [2]. Additionally, the surgeon must pay attention to previous scars in the same anatomic location as a planned surgery and be mindful of disrupted vascular connections that could lead to untoward outcomes.

Patients generally have many anatomic areas that require correction. Patients need to delineate the areas they would like addressed to the surgeon and together formulate a schedule. The authors' recommendation is to start with patients' highest priority and move down their list. Staging procedures may be required to minimize the operative time and avoid opposite vectors of tension. Some combinations of procedures can be performed safely and expeditiously, whereas other combinations are advised against. Procedures commonly combined include abdominoplasty with mastopexy, upper body surgery with lower extremity surgery, and lower body surgery with upper extremity surgery.

Markings

Patients should be marked preoperatively in the holding area, which is a good time to review with patients the location and length of the scars. Although all resection margins are marked preoperatively, the authors' recommendation is to commit to one line at the start of the procedure and dissect toward the other, only committing to the second margin after confirming that closure will be possible.

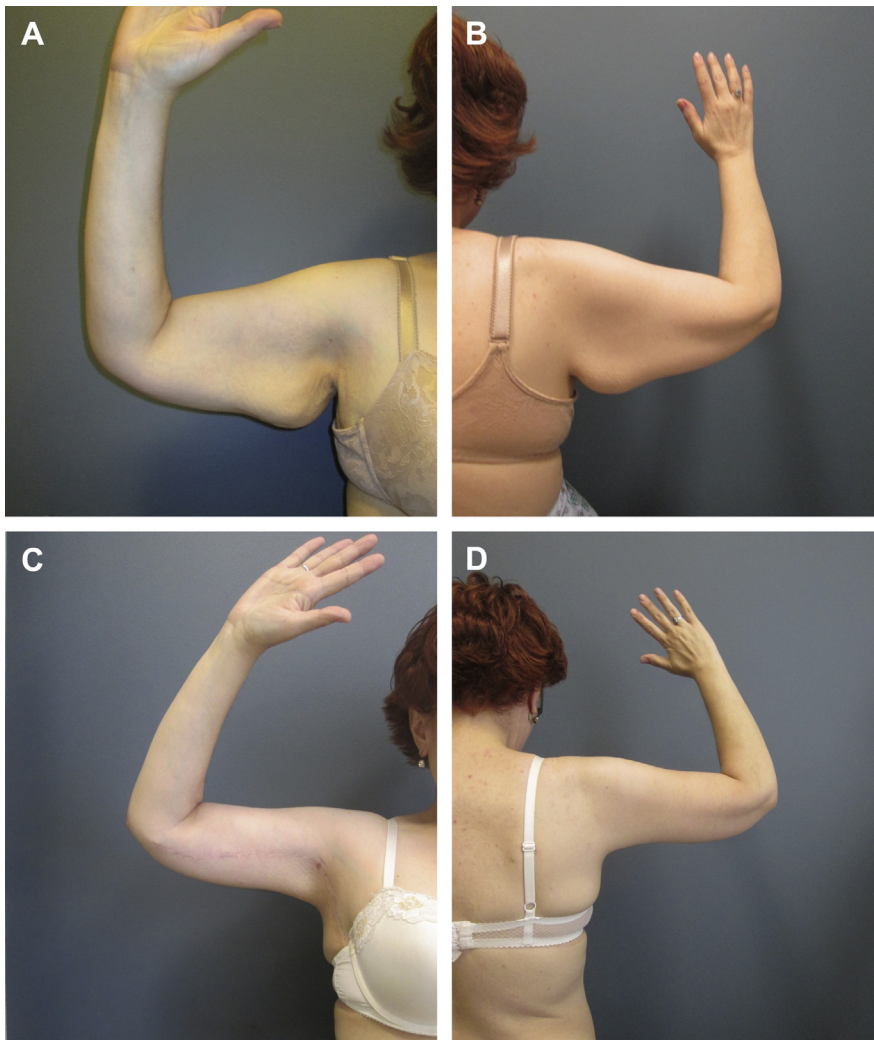


FIG. 2 A 50-year-old woman with a 45-kg weight loss after laparoscopic Roux-en-Y gastric bypass surgery (left: **A, B**) before and (right: **C, D**) 7-months after brachioplasty.

Prep and Patient Positioning

Appropriate patient preparation includes attention to venous thromboembolism (VTE) prophylaxis, body temperature, antibiotic timing and duration, fluid shifts, and positioning in the operating room. All patients should have intermittent pneumatic compression devices in place before induction of anesthesia. Antibiotic prophylaxis should be administered and redosed according to the Surgical Care Improvement Project's guidelines. Chlorhexidine-alcohol is preferred as the surgical skin prep antibiotic of choice, as it has been shown to be more efficacious than povidone-iodine

[6]. Some surgeons prefer to prep patients while in the standing position and then move onto a sterile operating room table. Extremities should be prepped circumferentially to allow for easy movement and easy access to all areas, permitting liposuction of other regions of the extremity or the excision site itself.

It is known that hypothermia can increase post-operative complications in body contouring patients [7]. The most effective way to maintain normothermia is by prewarming patients with forced warm air for at least 15 minutes before the procedure [8]. Techniques that can be used intraoperatively include



FIG. 3 Markings for a thighplasty.

coverage of regions that are not within the zone of the surgical procedure, forced warm air, maintenance of an ambient room temperature of at least 21°C, and use of warm intravenous (IV) and irrigation fluids.

Intraoperative positioning is important in the prevention of VTE as well as in avoiding nerve and ocular damage. Bony prominences should be appropriately padded to prevent a pressure nerve injury. Knees should be gently flexed to 15° and shoulders abducted no more than 90°. When prone, the eyes should be well protected against pressure and the neck should be comfortably positioned in neutral alignment.

For procedures that require access to multiple sides of the body for contouring intraoperatively, there are several described options for positioning. The first and most commonly reported begins with patients prone and then turned to supine. A second option is to begin supine and then move to the prone position. Finally, a third involves 2 position changes, with patients in the supine and each of the lateral decubitus positions.

Arm

A brachioplasty removes skin in one of 3 axes: longitudinal, transverse, or a combination of both. In the MWL population, almost all patients will require a longitudinal resection. There are 2 common scar locations described: either along the medial aspect of the arm, within the bicipital groove, or posteriorly. Some prefer IV lines to be away from the upper extremities; however, this is not always possible. An easy solution is to place the IV distal to the elbow and wrap a towel or other sterile sheet around the forearm to prep it out of the field. Similarly, the blood pressure cuff may be placed on the contralateral forearm and draped out.

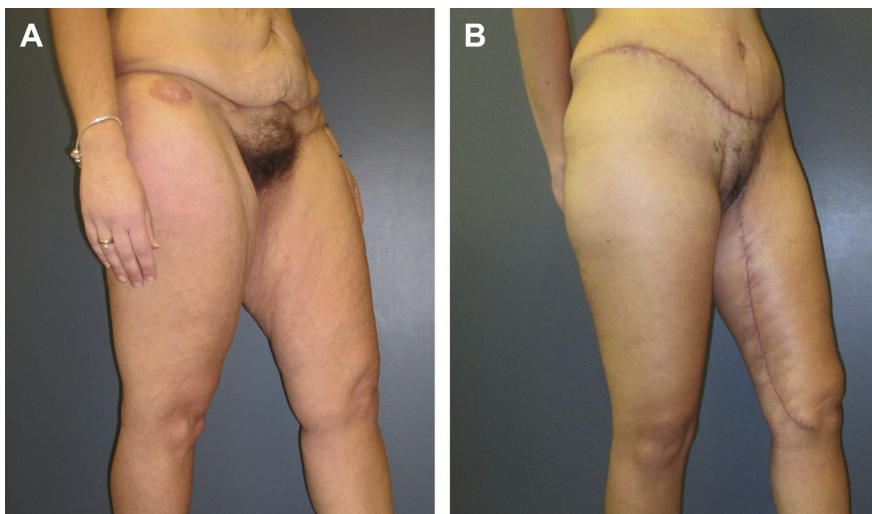


FIG. 4 A 41-year-old woman who lost 42 kg using diet and exercise (left: **A**) preoperatively and (right: **B**) 1 year postoperatively from thighplasty.

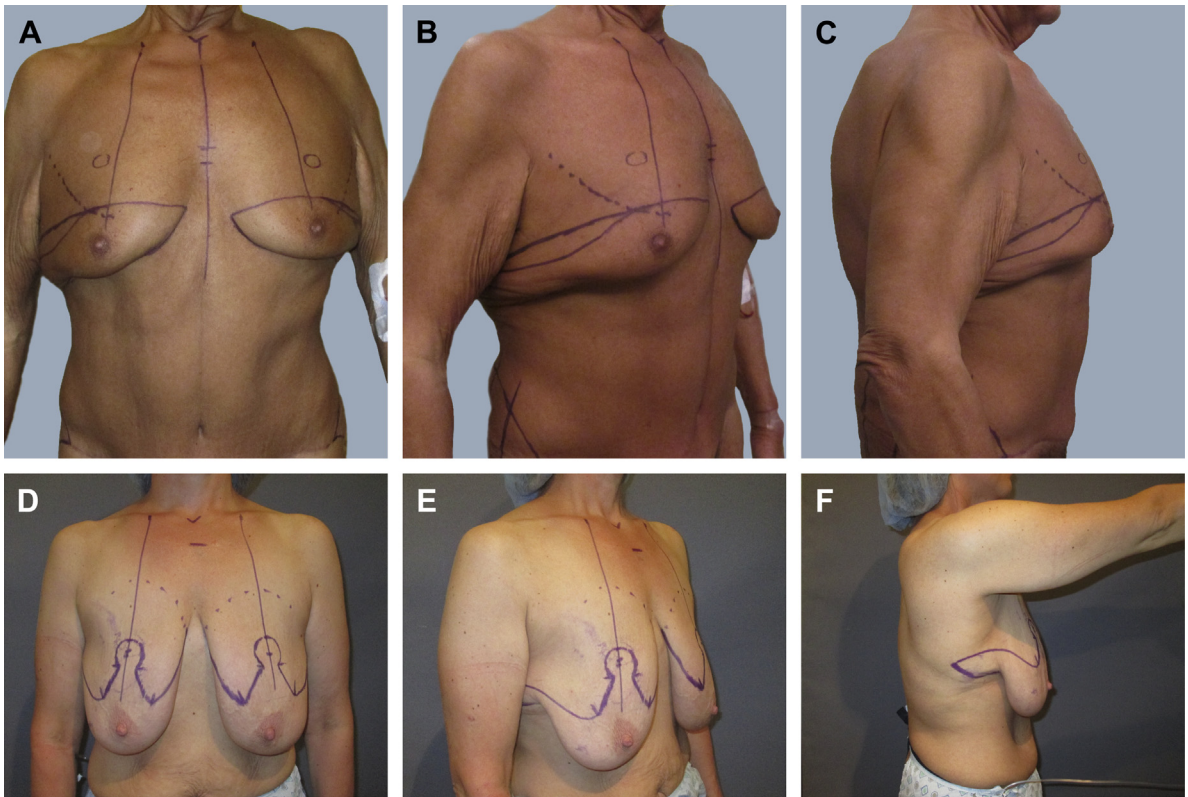


FIG. 5 Markings for correction of chest contouring in a (top: **A–C**) male and (bottom: **D–F**) female dermal suspension parenchymal reshaping mastopexy.

Markings

The markings are made with the shoulder abducted and elbow flexed at 90° angles. Pinch test determines the amount of tissue that can be safely resected; however, one must account for the thickness of the tissue between the fingers to allow for wound closure. Alternatively, a distraction test may be used to estimate the resection. In many patients, an extension of the brachioplasty must be made onto the lateral chest wall, sometimes as far inferiorly as to blend with a mastopexy incision. There is generally no need for a Z-plasty in the axilla in this cohort, as was previously performed.

Please refer to Fig. 1 for an example of markings for a brachioplasty and Box 2 for operative steps. An example of a medial brachioplasty is shown in Fig. 2.

Thigh

Similar to a brachioplasty, a thighplasty involves removal of skin in a longitudinal, transverse, or dual axis. The incision should stay close to the mons pubis

area to avoid scar migration and visibility in the upper thigh. The incision is placed either medially or laterally on the thigh, with medial far more common because it is more easily concealed.

Markings

The markings are made with patients supine and the lower extremities in the frog-leg position. Superiorly, at the level of the mons, the marking starts 4 cm away from the midline and extends within the groin crease because of the natural line that exists there. A longitudinal line is drawn along the adductor longus muscle down to the knee or past it if needed. Vertical excess is determined by sliding tissue along the adductor longus muscle and marking this location at the level of the groin crease. Horizontal excess is determined by pinch test or distraction test, shifting tissue from one side to the other to determine the extent of resection.

Please refer to Fig. 3 for example of markings for a thighplasty and Box 3 for operative steps. An example of a vertical medial thigh lift is shown in Fig. 4.

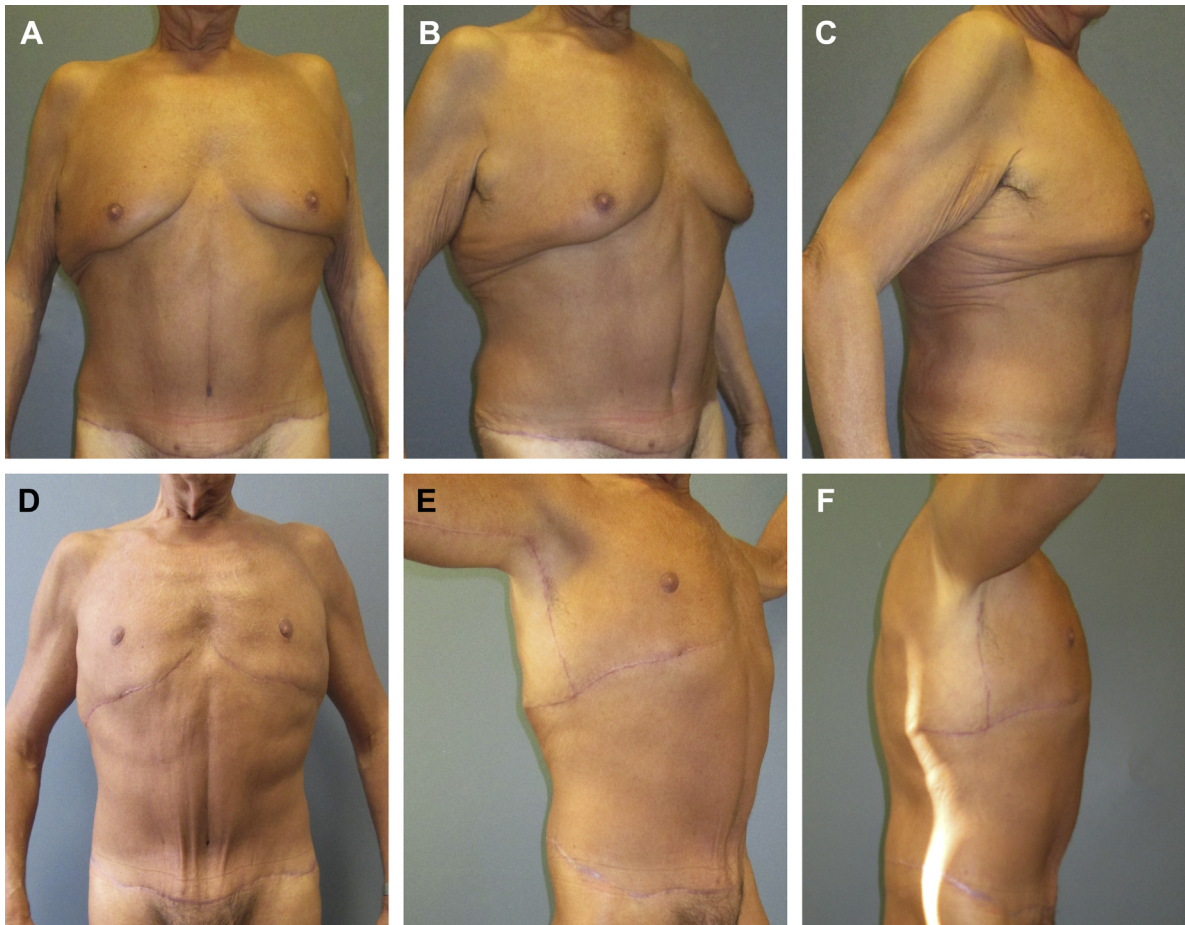


FIG. 6 A 67-year-old man who had laparoscopic Roux-en-Y gastric bypass surgery and subsequently lost 55 kg, (left: **A–C**) before and (right: **D–F**) 6 months after chest contouring with mastectomy and free nipple graft.

Some surgeons prefer to perform excision-site liposuction of the extremity, and a technique is outlined in Box 4.

Upper body

In patients who have lost weight following bariatric surgery, extensive procedures are required to restore a more anatomic shape in the chest and breast. For women, this involves a Wise-pattern mastopexy to treat a deflated, ptotic breast, whereas, for men, this means a pedicle-based procedure or mastectomy with free nipple graft to treat gynecomastia [12]. The upper body lift can blend nicely into a breast or brachioplasty incision.

Treatment of the male breast after MWL is similar to treatment of significant gynecomastia [13,14]. Depending on the amount of excess tissue and the location of

the nipple-areola complex (NAC), the deformity is addressed with the appropriate method that will place the NAC in the correct location and remove the excess tissue. Techniques include mastectomy through an inframammary fold incision or mastectomy with free nipple graft. A Wise pattern should be avoided to prevent coning of chest tissue.

Consideration must be paid to the characteristic breast deformities that appear after massive weight loss in a female, including a flattened appearance secondary to loss of fatty tissue, significant skin excess, and medialized nipple-areola complex. Generally, a Wise-pattern mastopexy or dermal suspension with parenchymal reshaping (DSRP) mastopexy is required to lift the breast superiorly and reshape the breast mound. DSRP should be avoided in women who have not had MWL, as too

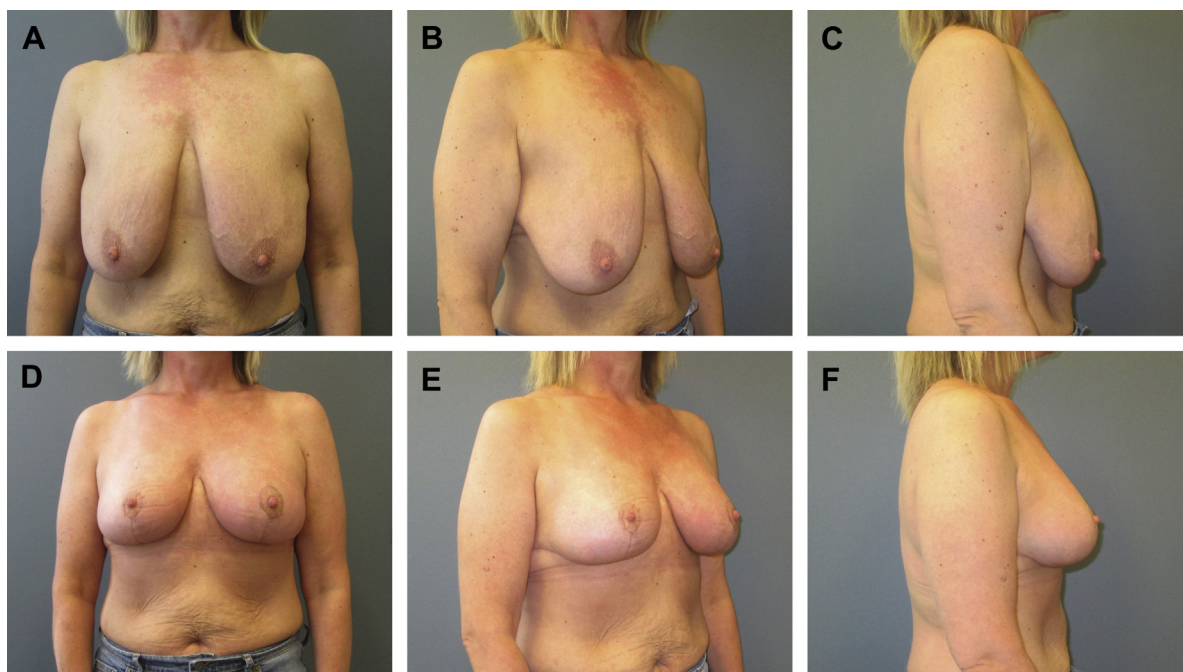


FIG. 7 A 42-year-old woman who lost 34 kg with diet and exercise. She later went on to have a dermal suspension mastopexy and is shown (left: **A–C**) preoperatively and (right: **D–F**) 6 weeks postoperatively.

much parenchyma can compromise the skin closure and lead to local wound healing problems. The mastopexy incision can also be used to correct abdominal wall laxity. Implants should be avoided in patients who have had weight loss surgery, as they are fraught with increased complications and are associated with recurrent early ptosis and implant malposition requiring

revision procedures. A mammogram should be obtained according to the latest recommendations before any procedure on the female breast.

Markings

Male

There are several treatment options available for male chest contouring, and markings are made according to the technique needed to correct the specific deformity. An example of markings for male chest contouring is shown in Fig. 5A–C along with pre- and post-operative photographs in Fig. 6.

Female

Markings are made just like a typical Wise-pattern mastopexy, and described later is the dermal suspension technique that is commonly used for this patient population.

Please refer to Box 5 for operative details. An example of markings for a dermal-suspension mastopexy is shown in Fig. 5D–F along with pre- and post-operative photographs in Fig. 7.

Lower body

The first determination to make is the type of lower body procedure that will best address patients' excess tissue.



FIG. 8 Diver's test showing excess abdominal tissue.

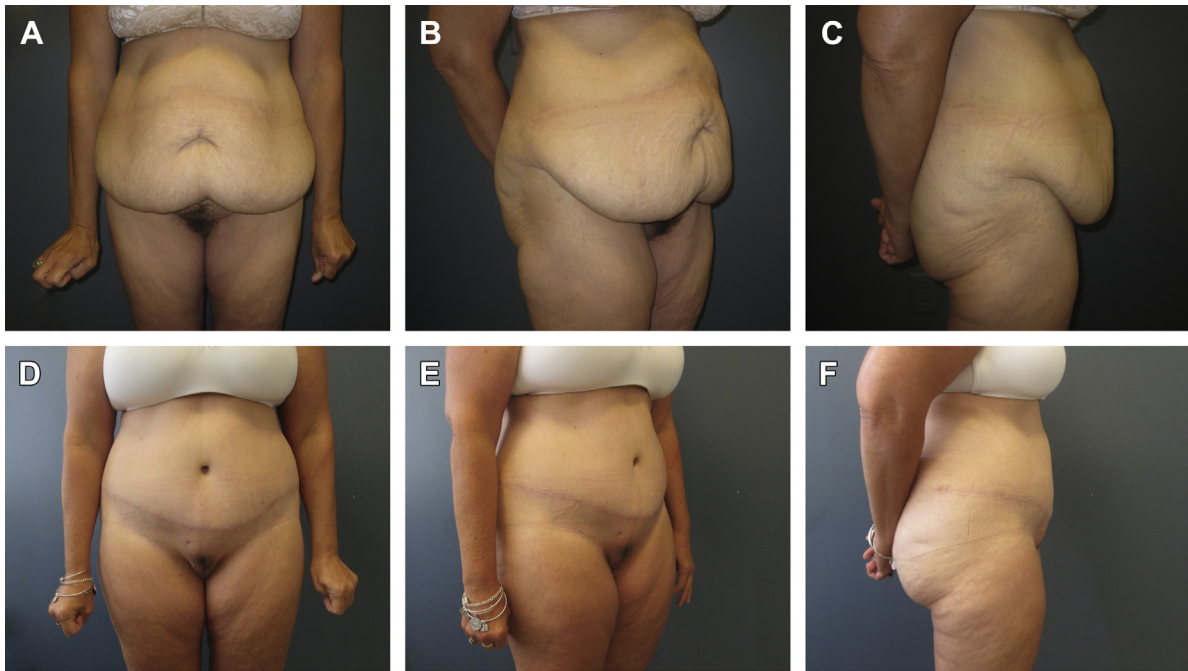


FIG. 9 A 52-year-old woman after 43-kg weight loss secondary to diet and exercise shown (left: **A–C**) before and (right: **D–F**) 1 year after abdominoplasty.

There are both anterior and posterior deformities that must be considered. The anterior assessment begins with a thorough physical examination of the abdomen. The surgeon must carefully evaluate the amount and location of excess skin, subcutaneous fat, and rectus diastasis as well as the presence of abdominal wall hernias, skin quality, intra-abdominal fat content, and previous scars. Fig. 8. demonstrates a technique to help the surgeon determine

BOX 1

These Questions Can Quickly Rule Out High-Risk Patients Who Need Further Workup or Referral to a Specialist Before Proceeding with Surgery

- Do you have a personal or family history of blood clots or bleeding?
- Have you ever had a heart attack or stroke?
- Can you walk up a flight of stairs without getting short of breath?
- Do you smoke? If no, inquire about vaping, dipping, chewing, or use of tobacco cessation products.
- Do you have a history of wound healing problems or infection (eg, methicillin-resistant *Staphylococcus aureus*) after surgery?

the amount of excess abdominal tissue. It is important to consider existing scars when deciding what type of procedure to perform and areas, if any, of undermining or liposuction. In patients who have had adjustable gastric banding surgery, one must be mindful of the location of the port with any abdominal wall procedure.

There are several different abdominoplasty types described, ranging from simple liposuction to a circumferential lower body lift. Liposuction only and mini-abdominoplasty techniques will not adequately address the skin laxity present in this population. For the purposes of this article, only those procedures that address this patient cohort in a cosmetic fashion are discussed. A true panniculectomy simply involves a wedge resection of lower abdominal tissue below the level of the umbilicus [15]. This procedure is performed for functional and not aesthetic purposes; therefore, it is not included in this discussion. Of all aesthetic surgeries performed, abdominoplasty carries the highest risk of VTE [16,17]. Patients should be apprised of the risk and all precautions taken to decrease the risk before agreeing to proceed with surgery.

Posteriorly, the physical examination focuses on the lower back roll and buttocks. In the patients who have had weight loss surgery, the gluteal deformity includes

BOX 2**Operative Procedure Steps for a Brachioplasty****PROCEDURAL APPROACH: BRACHIOPLASTY**

1. A solution of 1:100,000 of epinephrine in normal saline is injected subcutaneously along the anterior margin of skin resection. Ideally, this should be allowed to instill for 5 to 10 minutes before an incision is made; this can be accomplished by injecting off the field as soon as patients are asleep, before prepping and draping.
2. The anterior marking is incised with a scalpel along its length.
3. Dissection proceeds posteriorly toward the opposite resection margin. Care must be taken not to overdissect past the posterior marking or risk raising a flap of tissue.
4. A thin layer of fat is left over the deep muscular fascia to prevent injury to any nerve structures, being careful not to injure the median antebrachial cutaneous nerve in the distal two-thirds of the arm. In the axilla, the dissection is much more superficial and is almost skin-only to prevent injury to lymphatic structures.
5. Ability to close should be constantly verified as dissection approaches the posterior margin. This confirmation can be done by dividing the tissue into fourths and verifying the margin of resection by reapproximating the edges with a forceps and towel clamp.
6. Infiltrate the posterior margin with the same epinephrine solution and complete the resection.
7. Hemostasis is performed, the wound irrigated, and the incision temporarily closed with either staples or towel clamps to prevent edema from compromising the closure. A drain may be placed if desired.
8. The superficial fascial system of the arm is secured to the clavipectoral fascia in the axilla with 2-0 absorbable suture to prevent loosening.
9. The deep superficial fascial system layer is closed with 2-0 absorbable suture.
10. The dermis is closed with 3-0 or 4-0 absorbable suture in the subcuticular layer.
11. Cyanoacrylate glue is used to seal the incision.
12. The arms are loosely wrapped from hand to shoulder with an Ace bandage (3M, Saint Paul, MN, USA).

BOX 3**Operative Procedure Steps for a Thighplasty****PROCEDURAL APPROACH: THIGHPLASTY**

1. A solution of 1:100,000 of epinephrine in normal saline is injected subcutaneously along the anterior margin of skin resection. Ideally, this should be allowed to instill for 5 to 10 minutes before an incision is made; this can be accomplished by injecting off the field as soon as patients are asleep, before prepping and draping.
2. The anterior marking is incised with a scalpel along its length.
3. Dissection proceeds posteriorly toward the opposite resection margin. Care must be taken not to overdissect past the posterior marking or risk raising a flap of tissue.
4. Care must be taken to avoid injury to the saphenous vein and lymphatic structures. In the groin, the dissection is much more superficial and is almost skin-only to prevent injury to lymphatic structures.
5. Ability to close should be constantly verified as dissection approaches the posterior margin. This confirmation can be done by dividing the tissue into fourths and verifying the margin of resection by reapproximating the edges with a forceps and towel clamp.
6. Infiltrate the posterior margin with the same epinephrine solution and perform resection.
7. Hemostasis is performed, the wound irrigated, and the incision temporarily closed with either staples or towel clamps to prevent edema from compromising the closure. A drain may be placed if desired.
8. The superficial fascial system of the thigh flap is secured to Colles fascia in the groin with 2-0 absorbable suture to prevent labial distortion.
9. The deep superficial fascial system layer is closed with 2-0 absorbable suture.
10. The dermis is closed with 3-0 or 4-0 absorbable suture in the subcuticular layer.
11. Cyanoacrylate glue is used to seal the incision.
12. The legs are loosely wrapped from feet to groin with an Ace bandage.

BOX 4**Excision-Site Liposuction Steps in Brachioplasty or Thigh Lift****EXTREMITY EXCISION-SITE LIPOSUCTION**

If excision-site liposuction is planned in the extremity, step 1 of the arm and thigh procedure is replaced with infiltration of tumescent solution within the anterior half of the estimated area of skin resection. As the area is deflated and closure tested, liposuction can move posteriorly until the surgeon has confirmed that the resection will allow for reapproximation of the wound edges to avoid infiltrating areas outside the zone of resection. Liposuction access sites should be within the safe margin of resection so that they are removed with the skin excision. Resection may also be performed with the avulsion technique as described by Knotts and colleagues [9,10]. Liposuction may also be performed outside the zone of resection and has been shown to be safe and effective [11].

loss of adiposity in the buttock, decreased buttock projection, buttock ptosis, and lengthening of the infragluteal fold [18]. When deciding on which procedure to perform, it is important to remember that the level of desired maximum projection of the buttocks is at the level of the transposed mons pubis, where it is considered most aesthetically pleasing.

An LBL is the combination of an abdominoplasty, lateral thigh, and buttock lifts with a scar placed at the level of the bikini line [19]. A belt lipectomy, conversely, simply involves a circumferential beltlike resection of tissue with a scar located at the level of the waistline, higher than that with an LBL [19]. The scar should end in a V at the posterior midline to preserve the sacral dimple [20]. With either procedure, however, the buttock can appear flattened without the addition of gluteal augmentation. A lower scar allows for more gluteal auto-augmentation tissue to be incorporated into the flap. However, patients must be made aware that auto-augmentation is associated with an increased risk of complications [21].

Markings: Abdominoplasty

Standard markings begin with the vertical midline; the midpoint of the horizontal incision is marked no less than 5 cm superior to the vulvar cleft. The lateral-most point of the incision is then marked at the level of the anterior superior iliac spine (ASIS). Patients are then asked to lift on the central panniculus with both hands and the midpoint and lateral marks connected symmetrically. The authors prefer not to mark the superior incision at this time, as it is more accurately determined by intraoperative verification.

BOX 5**Operative Procedure Steps for a Dermal Suspension Parenchymal Reshaping Mastopexy****PROCEDURAL APPROACH: DERMAL SUSPENSION MASTOPEXY**

1. A solution of 1:100,000 of epinephrine in normal saline is injected subcutaneously along the skin markings. Ideally, this should be allowed to instill for 5 to 10 minutes before an incision is made; this can be accomplished by injecting off the field as soon as patients are asleep, before prepping and draping.
2. The entire area of skin between the NAC and the exterior markings is de-epithelialized.
3. Breast skin flaps with a thickness of 1 cm are raised superiorly toward the clavicle.
4. The dermo-glandular pedicles are raised off the medial and lateral pectoralis fascia, so far as needed to allow for rotation of the flaps superiorly around the central pedicle. A 10-cm central pedicle is preserved.
5. The lateral flap can be modified as needed for size.
6. The central flap, which contains the NAC, is secured to the second or third rib periosteum at the meridian with permanent suture, depending on where the NAC will settle.
7. The lateral flap is secured 2 rib levels lower than the central flap; the medial flap is secured at one rib level lower than the central flap.
8. The medial and lateral flaps are secured to the central pedicle, and plication of the construct is performed to achieve a nice round shape. Symmetry between sides is assessed frequently.
9. The superior skin flap is redraped over the new breast contour. The NAC is released partially, but not circumferentially, to allow inset into its keyhole.
10. Closure is performed with an absorbable suture over a drain.
11. Cyanoacrylate glue is used to seal the incision.
12. The breast is wrapped or placed in a bra without an underwire for 5 to 7 days postoperatively.

After induction and intubation with general anesthesia, patients' arms are secured to arm boards and the table is tested to verify that it will flex at the hips. If liposuction is planned, it is preferred to do it first, followed by resection of the abdominal tissue.

Please refer to Box 6 for operative details. An example of an abdominoplasty is shown in Fig. 9.

REHABILITATION AND RECOVERY

Immediate Postprocedural Care

Patients should be encouraged to ambulate postoperatively on the evening of surgery, with assistance. Chemical prophylaxis should be based on patients' Caprini score. The Caprini risk-assessment model for VTE [22] has been validated for plastic and reconstructive surgery [23] and should be highly considered when planning surgical procedures on patients after weight loss. These patients are known to be at an increased risk of VTE, and risk factors should be sought out to determine the correct prophylaxis regimen.

Generally, patients spend 1 to 2 nights in the hospital, depending on the specific procedures performed and anatomic sites operated on. Antibiotic use and drain placement are left to the discretion of the surgeon.

If used, drains are maintained for about 1 to 2 weeks. Showering can start 24 to 48 hours postoperatively. Compression of operative sites is recommended for at least 6 weeks postoperatively, except when showering.

CLINICAL RESULTS IN THE LITERATURE

Patients who have had weight loss surgery who subsequently undergo body contouring procedures report an improvement in self-esteem, social life, and physical, work, and sexual activities [24,25].

POTENTIAL COMPLICATIONS/RISKS/BENEFITS/LIMITS

The most common complication after surgery for MWL patients is delayed wound healing and wound dehiscence. Most of these heal relatively well and with local wound care. Seroma is another common complication with these procedures in this population. This complication can be circumvented with drain use and can be controlled with serial aspiration. If drain output remains high after a few weeks, sclerosis can be performed using doxycycline or bleomycin in the clinic. If no

BOX 6

Operative Procedure Steps for an Abdominoplasty

PROCEDURAL APPROACH: ABDOMINOPLASTY

1. A solution of 1:100,000 of epinephrine in normal saline is injected subcutaneously along the skin markings. Ideally, this should be allowed to instill for 5 to 10 minutes before an incision is made; this can be accomplished by injecting off the field as soon as patients are asleep, before prepping and draping.
2. The lower marking is incised down vertically to the anterior abdominal wall fascia. If the incision is marked very low, one should bevel superiorly away from the inguinal region to avoid disruption to lymphatics.
3. Some subcutaneous tissue should be left laterally over the ASIS to decrease the risk of injury to the lateral femoral cutaneous nerve.
 - a. Some surgeons prefer leaving some fat over the anterior abdominal wall fascia to decrease the risk of seroma, whereas others find this unnecessary.
4. Dissection proceeds as superiorly as is needed but no higher than the costal margin.
5. Care is taken not to float the umbilicus, unless intended.
6. A central tunnel is made in the supraumbilical region for 2 reasons:
 - a. To create space for reinset of the umbilicus through its new location
 - b. To allow for rectus plication, should it be needed
7. The bed is flexed at the hips to 45° or as much as is needed to obtain closure.
8. The superior margin is checked, marked, and excised.
9. The umbilicus is inset at its new location, at the level of the iliac crest.
10. Closure is performed with progressive tension sutures or over drains.
11. Cyanoacrylate glue is used to seal the incision.
12. The abdomen is wrapped with a binder or other compression garment.

drains are present and after 3 rounds of aspiration the fluid collection continues to reaccumulate, a seroma catheter can be placed in the clinic.

The most dreaded complication is the inability to close the wound edges intraoperatively, which generally occurs for one of 2 reasons: over-resection or delay in closure allowing edema to settle in the tissues. If the appropriate precautions are taken as described earlier, this complication can be consistently avoided. Over-resection can be prevented by committing to one margin at a time and rapid closure by temporary means until permanent closure is performed.

More serious complications include hematoma requiring return to the operating room, surgical site infection, nerve injuries, and VTE. Late complications include lymphedema and problems with scars, such as widening or hypertrophy.

MANAGEMENT

Patients are seen postoperatively within a week of surgery. They are allowed to drive once they are off narcotic medication. The authors prefer to leave their initial postoperative compression dressing in place until seen in the clinic. If drains are used, patients are seen weekly until they are all removed; the authors' criterion is an output less than 30 mL per day for 2 consecutive days. Once drains are removed, patients may continue to use their postoperative compression dressing or are free to use a nonmedical compression garment of choice. Lifting is restricted to 5 kg for 6 weeks to decrease the risk of wound dehiscence. Knowledge of how to prevent and manage complications in this patient population is paramount, and the unexperienced surgeon should not tackle these cases without considerable experience.

SUMMARY/DISCUSSION

Future considerations in this patient population are outlined in Box 7.

BOX 7

Future Considerations for Surgical Refinements or Improvement in Massive Weight Loss Patients

FUTURE CONSIDERATIONS

- Methods to decrease minor wound healing complications
- Techniques to deal with recurrent skin laxity
- Comparative study of wound closure devices
- Solution for striae

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Nonsurgical Facial Rejuvenation



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KEYWORDS

• Fillers • Radiofrequency • Ultrasound • Lasers • Light • Combination

KEY POINTS

- Facial rejuvenation entails a multimodal approach in which the epidermis, dermis, and fat are comprehensively treated to balance chromophores, stimulate collagen production, and replete/deplete fat as needed.
- Laser/light devices or new-generation peels can clear the face from pigment, whereas radiofrequency/ultrasound can tighten it and volumetric fillers can replete loss age-related fat pads.
- Combination programs according to a patient's characteristics, goals, and budget are key to optimal clinical outcomes.

INTRODUCTION

Noninvasive facial rejuvenation has become the new gold standard for age prophylaxis, facial health, and antiaging. Patients are increasingly aware and knowledgeable about the multimodal approach they need to adopt to ensure their youthful glow, and physicians have abandoned the scalpel and embraced working with the new generation of topicals, fillers, and energy-based devices. Data from several agencies, such as the American Association of Dermatologic Surgeons and the American Society of Plastic Surgery, are testament to the fact that every year, men and women, regardless of their culture, ethnicity, or socioeconomic status spend millions of dollars on noninvasive procedures, such as laser treatments, fillers, and peels. Highly sought treatments span from injectable products, such as fillers/toxins; energy-based devices, such as radiofrequency, ultrasound, and lasers; and active cosmetics known as cosmeceuticals that include skin care, eye care, skin lightening, and scar care products. Both pa-

tients and physicians reap the benefits of noninvasive facial rejuvenation, which include increased safety, less pain and recovery time, and cost-efficacy. Despite the need for more outpatient visits, with noninvasive rejuvenation there are fewer risks due to evading surgery/anesthesia, disruption of life routine, and increased patient satisfaction for a natural look. To combat the aging process, which is complex and triggered by extrinsic and intrinsic factors, that result in manifestations such as discoloration, elastosis, deep wrinkles, laxity, inflammation, vascular lesions, tissue redistribution, and atrophy, one must enlist several distinct and complementary rejuvenation approaches. As the process of aging is multifaceted and the result of a combination of several biologic processes, it is expected that one therapeutic strategy cannot single-handedly address the diverse set of indications to which the patient is seeking a resolution. In this article, we describe the topical and energy-based modalities used to target chromophores, even skin tone, and stim-

Disclosure Statement: Nothing to disclose.

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ulate dermal remodeling, as well as the methodologies used to volumetrically restructure the face from fat pad atrophy.

TOPICALS

The main categories of topicals used and recommended for patients in their daily skincare regimen are sunscreens and products that contain new-generation cosmeceutical agents (antioxidants, stem cell extract, peptides). The author advocates an AM-PM approach, in which in the AM products should aim to protect against photodamage and provide hydration, whereas the evening products should mainly focus on reducing redness, pigment, and stimulating collagen remodeling. Aside from daily antiaging prevention and protection, careful compliance to a skincare regimen also can accelerate recovery and prevent side effects from any noninvasive aesthetic treatment (eg, erythema post laser).

The goal of sunscreens is to reduce UVA and UVB absorption by the skin, and according to the American Academy of Dermatology, applying Sun Protection Factor (SPF) of 30 or higher every 2 hours is recommended to prevent photodamage [1]. Several beauty/skincare products such as lipsticks and makeup incorporate SPF in their formulations; however, it is important to note that the SPF is commonly on the low side compared with sunscreens, and need to be complemented by a high SPF of 30 or more. Studies have shown that products with SPF15 block 93.3% of UV rays compared with SPF 30 that blocks 96.7%, which means that doubling the SPF factor reduces light skin penetration by half [2].

Skincare products containing retinol as an active ingredient have been shown through histologic studies to increase collagen in the papillary dermis by inhibiting matrix metalloproteinases and collagenases [3]. Retinol activates a plethora of biochemical pathways by binding and activating retinoic acid receptors and the retinoid X receptors, thus upregulating downstream growth factors including tumor necrosis factor, epidermal growth factor, and interleukin-1. Aside from skin remodeling, retinol also has been shown to decrease melanocyte/keratinocyte atypia, resulting in an improvement of skin tone and texture. Many dermatologists recommend topical retinol products as a first-line therapy for photoaging, with benefits seen typically 4 months after therapy [4]. Despite the benefits, it is important to forewarn patients about potential side effects, such as skin irritation, redness, dryness, scaling, stinging, and peeling, that subsides after 2 weeks of treatment initiation.

Alpha-hydroxy acids, composed of compounds such as glycolic acid, lactic acid, citric acid, and salicylic acid have been shown to cause desquamation of the stratum corneum, which leads to increased glycosaminoglycan and collagen deposition [5]. Their side effects are mild and include stinging, burning, pain, and erythema.

Antioxidants are one of the most popular categories of cosmeceutical ingredients because they combat free radicals, a major cause of skin aging. The primary sources of cosmeceutical antioxidant ingredients are botanic extracts, because all plants must protect themselves from oxidation as a result of UV exposure by quenching reactive oxygen species [6]. Some antioxidants have additional functions, such as reduction of pigment and erythema (ascorbic acid, vitamin E). Studies have shown that antioxidants work best together, and not as singular agents. Thus, for example, a combination of topical vitamin E and vitamin C was more effective in reducing UV-induced erythema than each agent alone [7]. Other categories of antioxidants with antiaging properties include polyphenols (grape seed, coffee berry, green tea) and flavonoids (soy, blackberry, pycnogenol, ginkgo) [8].

Growth factors and stem cell extracts are also incorporated into skincare products with the main goals of stimulating collagen production and reducing any aberrant microinflammation. Key growth factors, also found in stem cell extracts, include platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor- β , and epidermal growth factor. They are derived from a variety of sources, including humans, animals, plants, recombinant bacteria, and yeast [9,10]. Commercially they are available in various topical formulations, such as a cell culture medium collected from a line of dermal fibroblasts originating from neonatal foreskin (NouriCel-MD; Allergan, Carlsbad, CA) and a formulation of processed skin cell proteins comprising a mixture of cytokines, growth factors, and antioxidants harvested from fetal fibroblast cell lysate (PSP, Neocutis; Merz, Lausanne, Switzerland), growth factors derived from the secretions of the snail *Cryptomphalus aspersa* are also commercially available (Tensage; Biopelle, Inc, Ferndale, MI).

CHEMICAL PEELS AND MICRODERMABRASION

Microdermabrasion treatments apply mechanical skin abrasion to remove the superficial layers of the skin. The device consists of an abrasive component and a vacuum that serves a waste receptacle for tissue debris.

Photoaging, correction of tone and texture, scars, and stretch marks have all been shown to be successfully treated with this technique. 6 to 8 weekly treatments are usually required for optimal clinical outcomes, and side effects are mild and self-resolving (erythema, mild pain) [11–15].

Chemical peeling as the name suggests, uses varying strengths of acids that can access different skin depths to decrease keratinocyte adhesion, and remove damaged epidermal tissue. Acids such as α -hydroxy acids, β -hydroxy acids, β -lipohydroxy acids, and tretinoids are commonly used. Thus far, indications for chemical peeling include photoaging, scars, pigmentary lesions, and acne [16–18]. The main types of peels are superficial, medium, and deep. Superficial peels exfoliate the epidermis without destroying the basal layer, medium peels penetrate to the papillary dermis, and deep peels reach the dermis. Depending on the strength and depth, there is a concomitant degree of severity in terms of recovery time, side effects, and results. It is critical before performing any treatment to evaluate the patient's skin type, thickness, and sensitivity. Typically, when using chemical peels, a priming phase of daily tretinoin therapy for a month before the peel is required to enhance penetration, and daily sunscreen use to prevent postinflammatory hyperpigmentation. Glycolic acid, Jessner solution, trichloroacetic acid (TCA) 10% to 15%, and tretinoin are the most commonly used superficial peels. Aside from stimulating remodeling and chromophore reduction, they also have anti-inflammatory, antibacterial, and antifungal properties. Medium-depth skin peels, such as 35% TCA, treat photoaging, lentigos, pigment lesions, and atrophic scars. Because they cause more burning sensation than superficial depth peels, a numbing agent can be sometimes applied to increase patient comfort. Deep peels are usually used for more severe photoaging and scarring, as they penetrate to the dermis and can restore the dermal architecture to a more native state. Due to the level of pain, treatment with deep peels requires general anesthesia or deep sedation; thus, they are rarely used nowadays as a first-line option for any aesthetic indication.

ULTRASOUND

Microfocused ultrasound (MFU) devices are very popular for tightening and lifting the skin, without the need for any surgery. The mechanism of action is based on the delivery of focused ultrasound waves to the dermal and subcutaneous layers (up to 5 mm), that induce thermal coagulation, triggering an

inflammatory cascade that leads to collagen/elastin and elastic fiber synthesis. The main commercially available device, Ulthera (Merz, Raleigh, NC), combines MFU with high-resolution ultrasound imaging, to enable visualizing tissue planes to a depth of 8 mm and to allow treatment control [19]. Ulthera has been FDA-cleared for application on the face, neck and chest, and is quite a popular treatment, as only 1 to 2 treatments are required, there is minimal downtime/pain, the effects are durable, and because it can be combined with other modalities, such as fillers for synergistic clinical outcomes. Currently available transducers emit frequencies of 10.0 MHz, 7.0 MHz, and 4.0 MHz with focal depths of 1.5 mm (dermis), 3.0 mm (deep dermis), and 4.5 mm (subdermal tissues), for use in patients depending on their goals and degree of skin laxity.

RADIOFREQUENCY

Radiofrequency (RF) devices have evolved dramatically over the years, and can address a spectrum of aesthetic indications, such as skin laxity, photoaging, scars, and mild vascular/pigment lesions [20–26]. Similar to ultrasound, the mechanism of RF action is the delivery of focused electromagnetic waves that generate thermal energy upon meeting tissue impedance. Subsequently, a biological cascade of events that includes collagen contraction, coagulation, and remodeling is initiated that ultimately leads to an increase in dermal thickness without affecting the epidermis. As melanin is not affected by RF treatment, these are safe for all skin types. Common adverse events include treatment-related pain (primarily with monopolar modalities) and transient erythema. Depending on the number of electrodes, RF devices can be classified into unipolar, bipolar, multipolar, or fractional. Unipolar devices have a single electrode with a grounding pad, and achieve bulk heating with deep tissue penetration. Contact cooling has been added to these devices (Thermage; Valeant, Laval, Canada) to decrease the treatment-associated pain. Bipolar devices consist of 2 electrodes that emit a fast, alternating current, and although they have an improved patient comfort profile, their efficacy is somewhat compromised [25]. It is common for this reason to combine bipolar RF with other sources of energy within the same device, such as light, lasers, ultrasound, vacuum, and pulsed electromagnetic field [25]. Other types of RF devices are the multigenerator ones (3DEEP; Endymed, Caesarea, Israel), that have multiple generators that increase their capacity to penetrate deep tissue across a larger anatomic area. The newest generation of

RF devices are nanofractional (Viva; VenusConcept, Toronto, Ontario, Canada), temperature-controlled, and microneedle RF (Intensif RF; Endymed). There are several high-level evidence-based clinical studies that show RF treatment can address a variety of indications, with good clinical results and no adverse effects or downtime. The number of treatments depends on the indication and the device used; for example, a patient with mild laxity will require 2 to 3 treatments over 3 months to notice improvement in skin tightening, whereas deep atrophic acne scars require 8 to 10 monthly treatments with nanofractional or RF-microneedling devices.

LASERS

Lasers and Light Devices

Laser and light treatment were the go-to treatments of choice for facial rejuvenation of aged/photoaged skin, before the introduction of MFU and RF devices. The main light/laser platforms include ablative and nonablative lasers of both the fractionated or nonfractionated type. Whereas nonablative lasers, are safer, and leave the skin intact, ablative lasers vaporize tissues and are more aggressive. Fractional lasers selectively create microthermal zones of ablation, whereas nonfractional lasers act on an entire surface-treated area [27,28]. The choice of laser/light device depends on the patient's skin type, indication, budget, and lifestyle. Numbers or treatments/interval and settings are not discussed because they vary depending on individual and practitioner.

Intense pulsed light (IPL) emits noncoherent polychromatic light in a spectrum of 515 to 1200 nm, and

can target melanin, hemoglobin, and water, resulting in selective tissue destruction and subsequent remodeling. These devices come with cutoff filters that can target specific chromophores, to treat indications such as vascular lesions or diffuse pigmentation. IPL devices are ideal for young patients with mild photoaging who desire a quick "photofacial," as it is commonly called. Care must be taken with patients of darker skin types, as undesirable side effects such as hypopigmentation may occur. IPL is safe and efficacious as several clinical studies have documented, and most patients achieve the desired clinical result [29–31]. Newer generation IPL devices like the Venus Versa (VenusConcept) or Limelight (Cutera, Brisbane, CA) have cooling mechanisms for patient comfort, and deliver more energy with faster pulses for increased safety and efficacy (Fig. 1).

Lasers in the visible and infrared spectrum are usually used to target specific vascular targets, pigment, and global rejuvenation. The KTP laser (532 nm), such as the Excel V (Cutera) is commonly used for superficial vascular lesions (facial spider veins, telangiectasias), as it absorbs oxyhemoglobin (Fig. 2). This laser is frequently frequency doubled with the Nd:YAG 1064 nm laser to target deeper vascular, and pigment lesions and for patients with darker skin types. In Q-switched mode, this laser produces 2 high-intensity short-pulsed wavelengths, 1064 nm and 532 nm respectively, for increased safety and efficacy. The flashlamp-pumped pulsed dye laser (PDL, 585–600 nm) is also used to treat not only vascular lesions but also inflammatory skin diseases, such as psoriasis, acne vulgaris, lupus, rosacea. The PDL shows some superiority compared with the KTP laser in terms of side effects, as treatments are not followed by the formation of



FIG. 1 A 65-year-old man before (*left*) and 3 months after (*right*) 1 treatment with Venus Versa (515 nm) for photoaging. (Courtesy of Venus Concept, Toronto, Ontario, Canada; with permission.)



FIG. 2 A 30-year-old woman before (*left*) and 1 month after (*right*) 1 treatment with Excel V (532 nm). (Courtesy of Cutera Research, Inc, Brisbane, CA; with permission.)

purpura [32,33]. The alexandrite laser delivers energy at the 755 nm wavelength, and has been used in a variety of indications, from vascular lesions, to pigment, photoaging, and scars.

The most significant innovation in these nonablative platforms is the introduction of picosecond pulses, that allow delivery of high energy in ultra-short pulses, decreasing the number of required treatments and side effects. Picosecond laser pulses promote subsurface laser-induced optical breakdown, leading to nonthermal, photoacoustic subsurface ablation. All of the currently available picosecond lasers, Picoway (Syneron-Candela, San Francisco, CA), Picosure (Cynosure, Westford, MA, USA), Enlighten (Cutera), and PiQ4 (Lumenis, Dreieich, Germany), are equipped with an additional specialized optical handpiece, a diffractive lens, that attaches to the fixed laser handpiece (Fig. 3). This lens can redistribute energy allowing multiple passes to be used to treat an area safely. These new technologies have been successfully used to treat rhytides, epidermal/dermal pigmented lesions, melasma, and acne scarring.

Fractional lasers include the nonablative Fraxel 1500 nm, 1927 nm, or ablative Er-YAG 2940 nm and CO₂ 10,600 nm, commonly used for global facial rejuvenation, fine lines, rhytides, scars, and pigmentation. Ablative fractional lasers are used for more severe cases of photoaging/aging and require a few days of downtime because vaporization of the epidermis can result in scattered bleeding and reepithelization [34]. Nonablative laser procedures are usually uncomplicated and popular among the younger-aged patients. Fractional lasers have been used in all types of skin, however in cases of skin types IV to V, lower treatment densities, epidermal cooling, pausing between passes of resurfacing lasers to reduce bulk heating are among best practices [35].

Volumetric Fillers and Neurotoxins

Key strategies for facial rejuvenation include neurotoxin and soft tissue filler injections. By weakening the muscles responsible for causing wrinkles when they contract, a youthful rejuvenated look can be achieved. Although neurotoxins do not per se stimulate collagen



FIG. 3 A 38-year-old woman before (*left*) and 6 months after (*right*) 2 treatments with Enlighten (1064 nm). (Courtesy of Cutera Research, Inc, Brisbane, CA; with permission.)

synthesis leading to increased dermal thickness, they reduce the amount of muscle movement and thereby may decelerate the rate of collagen breakdown. Neurotoxin injections can be performed in the upper (crow's feet, glabellar lines, forehead) and lower face. The choice of neurotoxin and area in which the injections are performed depend on the patient's goals, gender, and specific facial anatomy. For example, men typically require more neurotoxin than women, because they have larger musculature, but not so much as to lead to feminization. Some patients want to appear more natural and youthful, whereas others request specific cosmetic tweaks, such as brow elevation [36].

With regard to soft tissue filler injections, today's physicians are equipped with a myriad of options to treat their patients, and new-generation fillers continue to make their way in the market every year [37–39]. All filler formulations fall in 3 categories; biodegradable such as hyaluronic acid, semi-permanent such as calcium hydroxylapatite (CaHA), poly-L-lactic acid (PLLA), and permanent such as polymethyl methacrylate (PMMA) (Fig. 4) [40]. The choice of filler depends on the degree of patient lipoatrophy, and their specific desires. For example, some patients want one-and-done treatments, so a permanent filler would be the choice for them, given there are no physician-noted contraindications [41]. There are products from all soft tissue

categories that are appropriate and heavily used for pan-facial volumization. In addition, fillers like PLLA and CaHA also have biostimulatory properties, meaning they have been shown to induce a tissue response that triggers tissue remodeling, collagen production leading to improved skin quality, and increased dermal thickness [42].

The recommended technique to volumetrically structurally rejuvenate the face in patients with fat pad depletion is the bimodal trivector approach. The first step when performing the bimodal trivector approach involves supraperiosteal injections in the upper, middle, and lower face, thus re-introducing to the face a structural platform by mimicking the volume lost. Following these deep injections, areas of superficial lipoatrophy are treated via customized deep dermal/subcutaneous injections. The goal of these injections is to individualize the volumetric filling in accordance with patient preferences and desired outcomes [43].

Bringing It All Together with Combination Approaches

More often than not, patients seek to revitalize their face, and address issues of photoaging, dyschromia, loss of tone, rhytides, laxity, and volume loss. In short, they seek to reverse the signs of aging together with setting goals of personalized cosmetic tweaking that



FIG. 4 A 52-year-old woman before (left) and 12 months after (right) 2 treatments with Bellafill. (Courtesy of Suneva, Santa Barbara, CA.)

they feel will lead to the best aesthetic version of their own self. The current trend in the clinical arena is that of a multimodal approach, that exploits several different procedures to treat multiple tissues that are

involved in the manifestation of various skin concerns. A growing amount of evidence indicates that this new trend is indeed the most efficacious for both the patient and the treating clinicians [44–47]. Nevertheless,

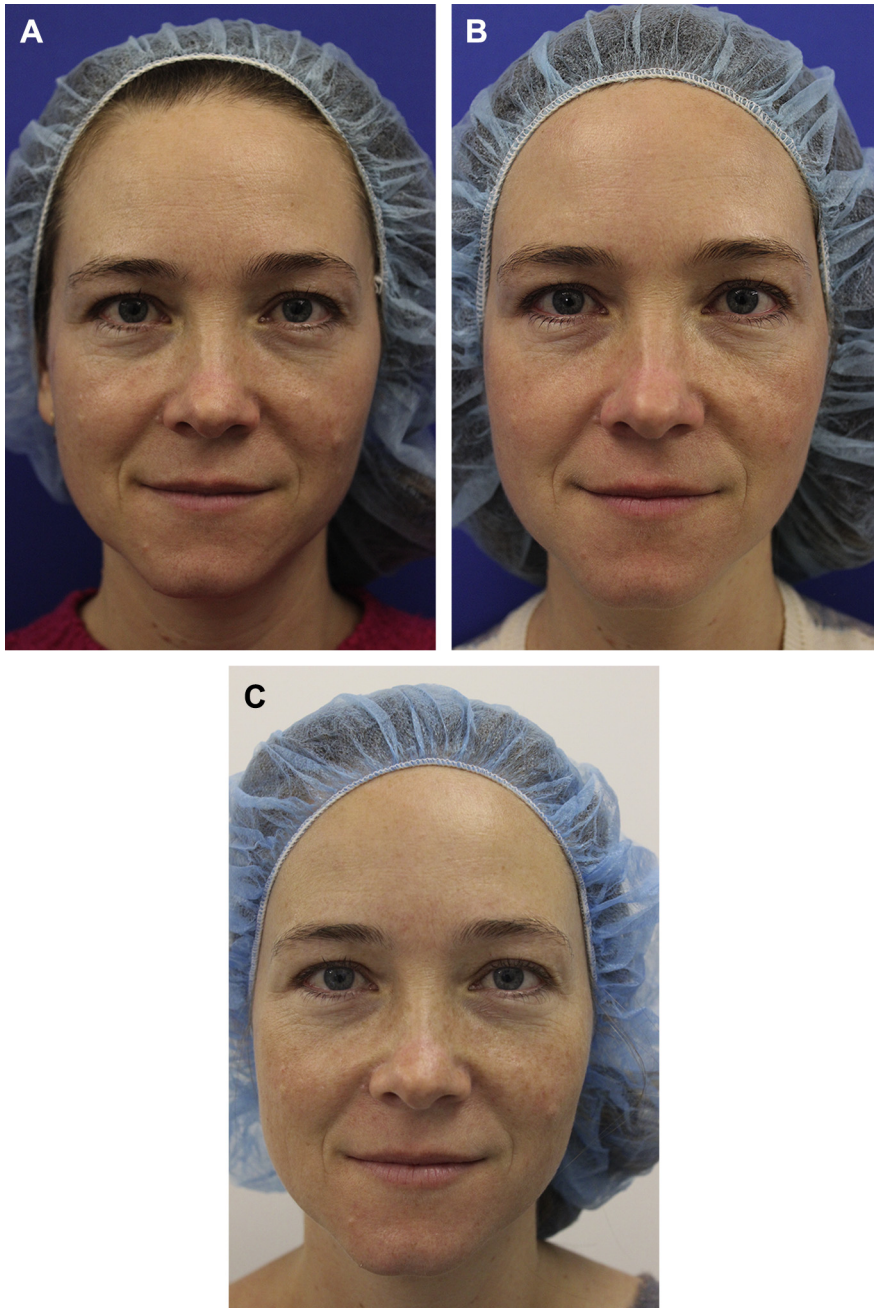


FIG. 5 (A) A 38-year-old woman at baseline, before any treatments, (B) 2 weeks after CO₂ treatment, and (C) 7 weeks after the completion of the 6 Venus Legacy treatments.

designing effective treatments requires strategic thinking by the clinician and thoughtful accounting for the patient's individual budgetary and time constraints. It relies on a change of thinking from viewing the patients as a snapshot in time, to a holistic continuum that will be shaped over time. Combination aesthetic treatments are integral to achieving successful facial rejuvenation (Fig. 5). Treatments can be done the same day but also staged at regular intervals, especially when performing treatments such as fractional laser ablation that is anticipated to result in swelling and erythema. Combining energy-based devices with each other are most successful when they do not overlap in the mechanism of action (thermal with nonthermal), and when they do not target the same tissue layers (epidermis vs subcutaneous fat). Together with fillers/toxins and topical cosmeceuticals, always in the context of a healthy lifestyle in terms of activity and nutrition, these regimens are anticipated to simplify over time and become an indispensable part of a patient's youth and well-being. Carruthers and colleagues [46] recently published their consensus recommendations for combined aesthetic treatments in the face using neurotoxins, fillers, and energy-based devices.

SUMMARY

Facial rejuvenation is a goal that can be achieved by patients from all walks of life, regardless of their age and aspirations. There are a surplus of treatment modalities that can be combined in several different ways to offer patients a variety of options to choose from and to tailor to their lifestyle and budget. As always, physicians practicing in the aesthetic field need to stay abreast of technological developments, new techniques, and best practices to best treat our patients. Participation in continuing medical education is paramount in this field, as is the reporting and publication of clinical findings.

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Radiofrequency with Microneedling



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KEYWORDS

• Radiofrequency • Microneedling • Laxity • Wrinkles • Scars

KEY POINTS

- Skin laxity occurs as a result of intrinsic, or chronologic, aging, as well as extrinsic aging, including UV light exposure, pollution, and smoking.
- Radiofrequency delivers heat to the dermis, resulting in controlled collagen denaturation, dermal shrinkage, and neocollagenesis.
- When coupled with microneedling, radiofrequency devices elicit the wound-healing response and deliver larger amounts of heat deeper into the dermis, resulting in greater collagen remodeling.
- Radiofrequency with microneedling is effective and safe in improving skin laxity and texture; however, proper patient selection is paramount to treatment success.

INTRODUCTION

A common complaint of patients seeking rejuvenating procedures is the sagging appearance of the skin, or skin laxity. Skin laxity occurs through a combination of both intrinsic and extrinsic aging processes. Intrinsic, or chronologic, aging results in skin wrinkling, atrophy, and loss of subcutaneous fat, and bone resorption. Extrinsic, or external, factors such as damaging UV light, pollution, and smoking, also contribute to the aging process [1]. Collagen, mainly types I and III, represents approximately 75% of the dry weight of the dermis and 20% to 30% of its volume [2]. Fibroblasts generate new collagen, whereas matrix metalloproteinases (MMPs) degrade it, along with elastin. UV radiation and other intrinsic and extrinsic sources of reactive oxygen species upregulate the production of MMPs, resulting in accelerated skin aging [3]. Elastin comprises 4% of the dry

weight of the dermis and gives the skin its mechanical strength and ability to resist deformation, or elasticity [4]. Intrinsic aging causes atrophy of elastin fibers, whereas extrinsic aging such as UV light exposure causes a disorganization in the elastic fiber network, resulting in solar elastosis [5]. The vital role of elastin in maintaining the structure of the extracellular matrix is well established; even the slightest decrease in the number of elastin fibers results in significant changes in skin elasticity and strength, as is evident in conditions like cutis laxa [6–8].

The gold standard for correcting skin laxity and achieving tightening is surgical correction, such as rhytidectomy. Although consistently and uniformly effective, surgical procedures can be invasive, risky, costly, and inappropriate for some patients. As such, the demand for less invasive treatment modalities has

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increased along with a concomitant flourishing in the field of energy-based tightening, especially radiofrequency (RF). In this review, the authors first discuss the mechanisms of noninvasive skin tightening and rejuvenation overall. They then specifically discuss the histologic cutaneous changes induced by both RF and microneedling. Next, they highlight the clinical evidence behind fractional radiofrequency (FRF) and radiofrequency with microneedling (RFM) in improving skin laxity and texture. Finally, they outline the procedural details of RFM.

MECHANISMS OF SKIN TIGHTENING AND DERMAL REJUVENATION

A central mechanism by which cutaneous remodeling and skin tightening occurs in response to thermal energy is the resultant structural change in the collagen polymer. When a certain amount of heat is delivered to collagen, the structured collagen triple helix denatures into a disorganized coil pattern. Orthopedic studies evaluating joint capsular collagen have demonstrated the histologic effects on collagen from thermal energy [9]. The reportedly ideal temperature of 65°C for collagen shrinkage is derived from experiments examining the effect of heating on joint capsular tissue [10,11]. Investigators demonstrated that the threshold for shrinkage of bovine knee capsules was between 60°C and 62°C, the same temperature range at which collagen denaturation was noted on light microscopy of the specimens [11]. Hayashi and colleagues [10] found that temperatures greater than 65°C induce tissue shrinkage, and contraction progressed up to a temperature 80°C. Therefore it is evident that collagen contraction depends on both temperature and duration of heating.

When heated, the hydrogen bonds, crosslinks between lysine and hydroxylysine, and disulfide bridges within the collagen triple helix are broken and the helix unwinds into a haphazard coil [10,12–15]. Because of the heat-stable intermolecular crosslinks within the new collagen configuration, the coil maintains its shape, leading to increased tension within the collagen as the structure shrinks and thickens [13,16]. Investigators have shown then even with rehydration of heated tissue the tightening effect is still maintained, demonstrating that tightening is not due solely to dehydrating tissue [17].

Thermal injury and superficial ablation of the skin trigger the wound healing response, thereby explaining the cutaneous rejuvenating effects these interventions have on the skin. The stages of wound healing include 3 phases: inflammation, proliferation, and remodeling.

During the inflammatory phase initiated by neutrophils and macrophages, fibroblast proliferation, type III collagen production, and keratinocyte proliferation are seen [18,19]. In the second week, during the proliferative phase, fibroblasts differentiate into myofibroblasts and cause tissue contraction of up to 40% [20]. Finally, during the remodeling period, after the third week, the overall collagen content of the dermis increases [18].

CUTANEOUS RESPONSE TO RADIOFREQUENCY

RF uses electromagnetic wave frequencies to generate an electric field within tissue to cause heating [21]. The amount of energy delivered to tissue is proportional to the current, time, and resistance within the tissue, also known as impedance. Tissue impedance is the main variable in the amount of heat delivered by the generated electric current. The mechanisms by which RF devices produce skin tightening are volumetric heating of the dermal structures, such as collagen and fascia, and induction of the wound healing response [22].

In one orthopedic study, RF was shown to cause tissue shrinkage in the femoropatellar joint capsule of adult sheep by collagen fibril shortening [23]. Zelickson and colleagues [24] demonstrated collagen fibril contraction and increased procollagen type I expression in bovine tendons and human skin similar to findings after treatment with ablative lasers. Another study demonstrated thickening of collagen in facial skin treated with RF [25]. As discussed, optimal treatment parameters depend on temperature as well as duration of treatment.

Few studies have evaluated the wound healing response after RF. Hantash and colleagues [26] studied the wound healing response of abdominal skin at various time points after treatment with an FRF device. Neocollagenesis, neoelastogenesis, increased cellularity, and de novo hyaluronic acid were observed.

CUTANEOUS RESPONSE TO MICRONEEDLING

The effects of microneedling on the skin were elucidated by Fernandes [27] in his study of percutaneous collagen induction. The study demonstrated that microneedling exerted its effects via the initiation of the wound healing response. The inflammatory phase ensues shortly after microneedles penetrate the epidermis and superficial dermis, causing focal damage to superficial blood vessels and collagen bundles, and the release of platelets

and neutrophils [27,28]. Within a few hours, epidermal microchannels rapidly heal by transepidermal migration of keratinocytes; however, needles with wider cross-sectional areas and occlusion can retard this process up to 40 hours [29,30].

The proliferative phase follows the inflammatory phase 5 to 7 days later, during which neutrophils are replaced with monocytes. These monocytes transform into macrophages that together with platelets release a cascade of growth factors [27,28]. Studies have shown that microneedling in mouse models upregulates expression of all 3 forms of transforming growth factor- β (TGF- β), especially TGF- β (a suppressor of scar formation) [31]. In addition, keratinocytes begin to reestablish the basement membrane by increasing laminin and collagen production, and a fibronectin matrix forms to align with fibroblasts and provide a scaffold for collagen deposition [27,28].

The remodeling phase can last from 8 months to 1 year. After 12 weeks, human and animal skin models treated with microneedling demonstrate significant increases in epidermal thickness and neoformation of collagens I, III, and IV [27,32,33]. Furthermore, the new collagen fibers are evenly spaced, unlike those seen with scars [32]. Collagen I gradually replaces collagen III, the primary type of collagen present in early wound healing. One study of histologic staining demonstrated a decrease in dermal elastin at 3 months, which was interpreted by investigators as a reorganization of aberrant fibers or even a decrease in solar elastosis [34]. The ultimate desired result of microneedling is tightening of skin laxity, smoothing of scars and irregularities, and improvement of wrinkles. These effects can last for 5 to 7 years [27].

FRACTIONAL RADIOFREQUENCY: THE EVIDENCE

Given the ability of microneedling and RF to improve skin laxity and texture as single modalities, the combination of these technologies promised deeper delivery of thermal energy and greater improvement in laxity as well as skin texture. The concept of fractionation has classically been applied to lasers, particularly resurfacing lasers such as the carbon dioxide laser. However, recently fractionation has been applied to RF as well. As discussed, RF uses electric current to produce thermal energy as it passes through tissue and meets resistance. FRF devices transmit current through electrodes in contact with the skin or via arrays of paired microneedles that penetrate the skin. These devices form closed circuits of bipolar current [35]. The devices, equipped

with electrodes, produce a pyramid-shaped pattern of thermal energy, with the smaller peak of the pyramid at the epidermis and the broader base of the pyramid deeper within the dermis [36]. The pyramidal pattern of heating results in large, yet safe, volumes of dermal heat delivery with minimal epidermal damage. Investigators have shown that less than 5% of the cutaneous surface is disrupted with one pass of the device [36]. The high temperatures at the level of the epidermis lead to focal, controlled epidermal ablation, while the dermis undergoes bulk heating and coagulative damage [36,37]. The intensity of the treatment and degree and depth of dermal heating can be tailored by adjusting the parameters such as energy level and coverage [37].

FRF has been successfully used for skin rejuvenation [36]. FRF can lead to improvements in skin laxity, texture, and wrinkles. Hruza and colleagues [37] showed that nearly 90% of patients exhibited improvements in skin tightness, smoothness, and wrinkling after 3 treatments, with approximately half of patients achieving an improvement of 40% or greater. Periorbital areas demonstrated the most improvement, whereas perioral sites showed the least improvement after treatment [37]. Because there is little epidermal disruption, FRF is generally not used for superficial pigment alteration [36]. However, studies have shown improvement in dyschromias and skin clarity [36,37].

Depending on patients' goals, most investigators recommend a series of 3 to 6 treatments to obtain optimal rejuvenation and patient satisfaction [36,37]. Maintenance of improvement can be achieved by undergoing an additional treatment every 3 to 4 months. Anecdotally, some clinicians use higher energies and densities in patients with lighter skin types and in older patients with increased baseline damage, while using lower energies and coverage in darker skin types [36,37]. In addition, when treating focal areas, there is less risk of sharp lines of demarcation between treated areas and nontreated areas, as has been noted with other energy-based fractional devices [36].

For acne scarring, 3 to 4 treatment sessions with FRF led to a moderate improvement of 25% to 75% [38]. Numerous reports on the effectiveness of FRF for acne scarring also demonstrated its safety in darker skin types with a relatively low risk of postinflammatory pigmentary alteration [39–41]. Although certainly effective for acne scarring, there is a dearth of head-to-head trials comparing FRF to more well-established treatments, such as ablative fractional lasers. Therefore, although FRF may not replace resurfacing lasers in the treatment of acne scarring, it may prove a useful adjunctive treatment modality.

FRF has also shown promise in the treatment of non-acne scarring. In an uncontrolled study of 95 patients with nonhypertrophic burn scars, investigators demonstrated significant improvements in cosmesis after 3 to 5 sessions at varying time intervals. There were improvements in the scar color, thickness, and pliability; however, no significant improvement was noted in vascularity, pain, or itch [42].

RADIOFREQUENCY WITH MICRONEEDLING: THE EVIDENCE

The effects of FRF on scarring and skin rejuvenation can be augmented by the use of RFM (Fig. 1). RFM devices contain either insulated microneedles that produce small spherical thermal injury zones with coagulative damage around the tip of the needle or noninsulated microneedles that produce larger cylindrical thermal injury zones with coagulative damage spanning the dermis [43]. The needles can be adjusted to reach depths ranging from 0.5 to 3.5 mm [44]. As discussed, the trauma of the microneedles alone initiates the wound healing response and an ensuing cascade of growth factors, leading to collagen production and deposition in the upper dermis [45].

Many studies have demonstrated the efficacy of microneedling alone in the treatment of acne scars as well as other scar types [46–49]. Three studies investigated the efficacy of RFM in the treatment of acne scars in 91 patients (Fitzpatrick skin types III–V) and consistently reported moderate improvement in scar appearance after treatment [44,50,51]. Ice pick and boxcar acne scars respond more readily than rolling scars [52]. Overall, RFM appears to offer

a more dramatic improvement in acne scarring than bipolar RF alone.

The role of RFM in skin tightening and rejuvenation has also been investigated. Six months after a single microneedle fractionated bipolar RF treatment, patients exhibited a 25.6% improvement in facial rhytides and a 24.1% improvement in facial and neck laxity [53]. Other studies have substantiated these findings [43,54]. For skin tightening, devices with noninsulated microneedles produce more effective skin tightening than the earlier, fully insulated microneedles, due to the deeper delivery of heat with each treatment [43].

Expected reactions associated with FRF and RFM include transient pain, redness, swelling, and mild superficial crusting that resolve within 3 to 5 days [38,49,51]. Transient postprocedure track marks have been reported after RFM (6%) [44]. Reported rates of postinflammatory hyperpigmentation are low (<3%) [39,41,51,55].

PATIENT SELECTION

As with any procedure or device treatment, proper selection of patients is of the utmost importance for maximizing outcomes. For the 2 most frequently documented indications for RFM treatment, acne scarring and skin laxity, particularly of the lower face and neck, proper selection can be the difference between treatment success and failure.

Improvement in acne scarring is a function of the dermal collagen remodeling that occurs following treatment. The capability of delivering heat directly to all levels of the dermis, while avoiding the potential complications of overheating the epidermis, is tailor made



FIG. 1 Patient demonstrating significant improvements in lower facial laxity and skin texture after 3 treatments with RFM with insulated needles.

to the treatment of acne scarring with all skin types. During the initial consultation, the type of lesions should be carefully noted. Depressed distensible and boxcar scarring morphology seems to respond best from the authors' experience. These lesions are rooted in dermal contour deformity due to volumetric loss secondary to inflammatory sequelae of papular and nodulocystic acne. Focal neocollagenesis in the mid and upper dermis can revolumize the affected dermis and improve the depressed appearance of these types of scars. Depending on the age of the scars, concurrent erythema and pigmentation may also be present. RFM typically does not improve these issues; as such, the patient should be made aware that other modalities, including treatment with vascular or pigment lasers, can be used for more global improvement, once the depressed component of the scar has been treated. Ice pick and hypopigmented scarring are 2 other types of scarring that can occur from acne. These types of scars typically do not respond well to treatment with RFM and are more amenable to other options, such as trichloroacetic acid and laser resurfacing.

Mild to moderate skin laxity, particularly of the lower face and neck, is another primary indication for RFM treatment. Again, patient selection is critical, because RFM is not usually effective for severe laxity. Some generalities can be made during the consultation: thinner skin seems to respond better than thicker, sebaceous skin and mild to moderate laxity is more responsive than severe skin laxity. Laxity and rhytides of the lower face (perioral, mid cheeks, jawline, neck) have been shown to respond readily, most likely due to their more "volume-depleted" nature and evolution from bone or fat loss in the face. Rhytides of the lower face contrast with those of the upper face (periocular and forehead rhytides), where dynamic muscle movement is more responsible for the formation of upper facial lines and wrinkles. One historically difficult area to treat, which has proven to be quite responsive to RFM in these authors' hands, is the concentrically shaped laugh or accordion lines of the mid cheeks. With multiple RFM treatments, enough dermal collagen and elastin rebuilds, improving the appearance of these lines long term, while not leaving any noticeable demarcation between the treated area and the rest of the cheek cosmetic subunit.

RADIOFREQUENCY WITH MICRONEEDLING: THE PROCEDURE

The procedure starts by obtaining adequate local regional anesthesia of the treatment area. Local anesthesia can be

accomplished in numerous ways, including topical, local, or tumescent anesthesia, in order of least to most invasive. The authors have evolved their technique over time from using more tumescent anesthesia and local nerve blocks to delivering more precision local anesthesia to the exact level of microneedle penetration and energy deposition, using a 3- to 5-needle array with 0.4- to 0.5-mm needles (Mesoram, Munchen, Germany). Following anesthesia, a single- to multi-pass regimen is used, with settings that vary the depth of needle penetration matching the depth of the lesion. For example, some RFM devices allow for energy deposition at 0.1- to 0.5-mm increments, so that the dermis of an acne-scarred patient can be treated at levels of 2.5 mm, 2 mm, and 1.5 mm in multiple passes. The incremental layering of heat allows for thermal injury in a zone in and around the depth of the acne scar, thereby presumably maximizing volumetric enhancement. For laxity or rhytides, the intervals may change to 3.5 mm, 2.5 mm, and 2 mm to effect more thermal injury deeper in the mid to deep dermis.

Postoperative care centers on the use of bland emollients (creams or ointments) to decrease transepidermal water loss and accelerate healing. Healing tends to be rapid because of the fractional nature of these treatments as well as the lack of need for reepithelialization (the epidermis is relatively spared). Bruising and/or edema can be present within 1 to 2 days of the procedure, but is typically self-limited.

SUMMARY

Skin laxity occurs as a result of intrinsic, or chronologic, aging, as well as extrinsic aging, including UV light exposure, pollution, and smoking. RF delivers heat to the dermis, resulting in controlled collagen denaturation, dermal shrinkage, and neocollagenesis. When coupled with microneedling, RF devices elicit the wound-healing response in response to microneedling and deliver larger amounts of heat deeper into the dermis, resulting in greater collagen remodeling. RFM devices are effective and safe in improving skin laxity and texture; however, proper patient selection is paramount to treatment success.

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Injectable Fillers

Comparison of Materials, Indications, and Applications

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KEYWORDS

- Injectable fillers
- Hyaluronic acid (HA) fillers
- Facial rejuvenation
- Facial volumization
- Minimally invasive aesthetics

KEY POINTS

- Treating facial aging continues to be a challenge for cosmetic surgeons and aesthetic physicians, but increased knowledge of the anatomic changes that occur with age and improved tools for rejuvenation enable achieving excellent aesthetic results in a minimally invasive way.
- There are 3 general classes of injectable fillers available: autologous (fat, dermis, and fascia), biologic (hyaluronic acid and bovine and human collagen), and synthetic (calcium hydroxyapatite, poly-L-lactic acid, and polymethylmethacrylate).
- Variations in the rheologic properties—elasticity, flexibility, viscosity, hydrophilicity, particle size, particle concentration, and cross-linking—have an impact on the clinical indications and applications of a particular filler.
- Facial volumization should be performed deep to superficial and cephalad to caudad, and the appropriate filler should be selected based on anatomic site, patient-specific goals and soft-tissue dynamics, and the properties of the filler.
- There must be awareness of the adverse effects and immediate, early, and late complications of injectable fillers and how to avoid and treat those complications.

INTRODUCTION

The approach to the aging face provides significant complexity and, at times, confusing challenges to the aesthetic physician and surgeon. As such, approaches have rapidly evolved throughout the recent decades. Cadaver and advanced imaging studies have demonstrated that skin, soft tissue, and bony modifications and volume loss are principal causes of facial aging. With the increasing popularity of noninvasive facial rejuvenation options, it has become essential for aesthetic practitioners to be knowledgeable and facile with soft tissue fillers [1]. This article discusses

the most common types of fillers, their unique characteristics, and specific clinical indications. This article focuses on technical considerations and pearls for rejuvenating specific aspects of the face, breaking them into thirds: the upper face, midface, and lower face. Finally, potential complications and how to avoid and treat them are reviewed.

HISTORY OF INJECTABLE FILLERS

Physicians have treated facial aging and volume loss for more than a century, as fat grafting to the face has been

Disclosure Statement: I. Percec serves as a consultant for Galderma. The other authors have nothing to disclose.

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reported as early as 1893 [2]. In the early 1900s, surgeons in Vienna injected liquid paraffin for facial rejuvenation but stopped soon after given the public backlash regarding the high rate of complications [2]. Throughout the 1900s, multiple synthetic fillers, including silicone oil and polytetrafluoroethylene, were explored with minimal success [3–6].

In the 1970s, dermal fillers made of viscous fluids or polymer particle suspensions were injected to treat acne scars, rhytides, congenital and traumatic soft tissue defects, Romberg disease, and HIV-associated lipodystrophy [7–13]. In 1981, a major step toward modern-day fillers occurred with the FDA approval of Zyderm and Zyplast (Inamed, Santa Barbara, CA), both bovine collagen fillers designed for cosmetic use [2]. Despite its success in treating fine rhytides, bovine collagen caused hypersensitivity reactions, which required preinjection skin testing and had a short duration of effect [2,14]. These disadvantages, coupled with the increasing awareness and fear of bovine spongiform encephalopathy, led to these injections only performed on a small subset of highly affluent patients [2,14]. The latest generation of facial fillers is composed of hyaluronic acid (HA), calcium hydroxyapatite (CaHA) and poly-L-lactic acid (PLLA). Continued innovations in facial fillers are aimed at developing longer-lasting and more natural products with fewer adverse effects and improved patient-reported outcomes.

Classification and Mechanical Properties of Fillers

Currently, there are 3 general classes of injectable fillers available: autologous, biologic, and synthetic. Autologous fillers include fat, dermal, and fascial fillers; however, this class of filler is not discussed in this article. The most commonly used biologic fillers worldwide are HA fillers. Other biologic fillers include bovine and human collagen. Synthetic fillers include CaHA, PLLA, and polymethylmethacrylate (PMMA), which is the only permanent filler (Table 1).

Although rheologic properties are primarily used to characterize HA fillers, all fillers can be characterized according to the following intrinsic properties: elasticity, flexibility, viscosity, hydrophilicity, particle size, particle concentration, and cross-linking. Variations in these parameters between fillers have an impact on the clinical indications and applications of a particular filler (Table 2). Elasticity (G') is a material's ability to resist compression and is a proxy for gel hardness, how much the gel is displaced given a degree of stress. Fillers with a high G' are typically firmer than those with low G' and are considered superior at lifting and deep volumization. Because

they feel firmer, however, high G' fillers may cause more tissue disruption in thin tissues. Fillers with a low G' commonly feel softer and thus are considered better for the treatment of thin tissues and superficial rhytides. Flexibility (xStrain) refers to how much strain a material can withstand and still be reversible before deformation, much like the flexibility of a rubber band before snapping. Highly flexible fillers with a high xStrain tend to be softer and diffuse more easily, making them ideal for use in thinner and more superficial tissues. Viscosity (n^*) is a material's ability to flow, spread, and resist shearing forces and have an impact on a filler's clinical effect in a manner similar to but distinct from that of G' . Finally, hydrophilicity is the product's capacity to attract water and expand, contributing to the degree of volumization and swelling.

There are 2 general classes of HA fillers, namely, monophasic and biphasic gels. Monophasic gels are cross-linked in 1 process to produce a stabilized smooth gel without particles. Biphasic gels are composed of cross-linked HA suspended in a liquid. For particulate fillers, particle size is determined by the polymerization of the glycosaminoglycan chains and straining techniques. Particle size contributes to the filler's lifting and filling power as well as to swelling capacity. Large particle fillers are better at filling deep folds and creating volume, whereas small particle fillers are better for moderate folds and areas of thinner skin. The particle size of the filler further contributes to minimum size of the injection needle. Some fillers are composed of small and large particle size cross-linked in a proprietary manner, whereas others are composed of a consistent particle size. Finally, increasing particle concentration and the degree of cross-linking both strengthen the durability of the filler and longevity of effect due to better resistance to enzymatic breakdown by the endogenous enzyme hyaluronidase. Rheological and particle properties all contribute to the clinical behavior of an HA filler and underscore the complexity of filler injection in relation to patient anatomy and tissue quality. Therefore, these factors must be understood by the injector for optimal, natural results.

TYPES OF BIOLOGIC FILLERS

Hyaluronic Acid

The most commonly used fillers today are temporary HA fillers. HA is a naturally occurring polysaccharide that is a critical component of the dermis and other tissues, and its depletion with advancing age contributes to the aging face phenotype. One of the benefits of an HA filler is that it increases soft tissue volume as a

TABLE 1

List of Food and Drug Administration–Approved Fillers, Their Manufacturers, Food and Drug Administration Approval Date, and Food and Drug Administration–Approved Indication

Filler	Manufacturer	Food and Drug Administration Approval Date	Food and Drug Administration Approval Indication
Juvederm Vollure XC	Allergan	2017	Moderate to deep facial wrinkles and folds: NLFs.
Restylane Refyne	Galderma	2016	Moderate to severe deep facial wrinkles and folds (NLFs) in people over 21
Restylane Defyne	Galderma	2016	Moderate to severe deep facial wrinkles and folds (NLFs) in people over 21
Juvederm Volbella XC	Allergan	2016	Lip augmentation. Correction of perioral rhytids in people over 21
Restylane-L Lyft	Galderma	2015	Moderate to severe facial folds and wrinkles or in patients over 21 who have age-related volume loss
Restylane Silk	Galderma	2014	Lip augmentation. Dermal implantation for correction of perioral rhytides in people over 21
Juvederm Voluma XC	Allergan	2013	Deep injection for cheek augmentation to correct age-related volume deficit in people over 21
Restylane-L	Galderma	2012	Moderate to severe facial wrinkles and folds: NLFs. Lip augmentation in people over 21
Belotero Balance	Merz	2011	Smooth facial wrinkles and folds, especially around the nose and mouth: NLFs
Juvederm Ultra XC	Allergan	2010	Addition of 0.3% lidocaine to Juvederm
Juvederm Ultra Plus XC	Allergan	2010	Addition of 0.3% lidocaine to Juvederm.
Sculptra Aesthetic	Galderma	2009	Shallow to deep NLF contour deficiencies and other facial wrinkles
Prevelle Silk	Mentor	2008	Moderate to severe facial wrinkles and folds (NLFs) in people over 21
Evolence Collagen Filler	OrthoNeutrogena (Los Angeles, CA)	2008	Moderate to deep facial wrinkles and folds: NLFs ^a
Artefill/Bellafill	Suneva (Santa Barbara, CA)	2006	Facial tissue around the mouth: NLFs.
Radiesse	Merz	2006	Moderate to severe facial wrinkles and folds: NLFs. Facial fat loss (lipoatrophy) in people with HIV. Hand augmentation to correct volume loss in dorsum of the hands (2005)
Juvederm	Allergan	2006	Moderate to severe facial wrinkles and folds: NLFs
Eleveess	Anika Therapeutics (Bedford, MA)	2006	Moderate to severe facial wrinkles and folds: NLFs
Sculptra	Galderma	2004	Facial fat loss (lipoatrophy) in people with HIV

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TABLE 1
(continued)

Filler	Manufacturer	Food and Drug Administration Approval Date	Food and Drug Administration Approval Indication
Captique	Inamed/Genzyme (Santa Barbara, CA)	2004	Moderate to severe facial wrinkles and folds: NLFs
Hylaform	Inamed/Genzyme	2004	Moderate to severe facial wrinkles and folds: NLFs
Restylane	Galderma	2003	Moderate to severe facial wrinkles and folds: NLFs. Lip augmentation in people over 21 (2011)
Cosmoderm	Inamed	2003	Soft tissue contour deformities: wrinkles, acne scars ^a
Fibrel	Serono	1988	Depressed cutaneous scars
Zyplast	Collagen	1985	Contour deficiencies ^a
Zyderm	Allergan	1981	Contour deficiencies of soft tissue ^a

^a Discontinued.

physiologic polysaccharide that is normally present within endogenous tissues. Furthermore, because it is biocompatible, biodegradable, and nonimmunogenic, HA is an ideal filling agent. Currently, all the HA fillers are synthesized via fermentation of *Streptococcus equi* bacterium. Specific preparation platforms are employed by different manufacturers, some of the most commonly known are nonanimal stabilized HA technology and XpressHAN (OBT) technology. Other

technology platforms, such as those based on the cross-linking of different particle size and properties, include Vycross technology, and additional platforms are regularly being developed. The reason such stabilized cross-linked HA preparations are necessary is that if the aqueous form of HA particles were directly injected into the tissue without additional manipulation, it would be rapidly metabolized by the endogenous enzyme hyaluronidase. Cross-linking

TABLE 2
Rheologic Properties of Select Hyaluronic Acid and Calcium Hydroxyapatite Fillers

Name	Hyaluronic Acid Concentration (mg/mL)	Lidocaine	Elasticity (G')	Viscosity (n*)	Relative Injection Depth
Belotero Balance	22.5	No	30	9217	Superficial
Juvederm Ultra XC	24	Yes	111	27,034	Superficial-medium
Juvederm Ultra Plus XC	24	Yes	136	32,152	Medium-deep
Juvederm Voluma XC	20	Yes	274	92,902	Medium-deep
Prevelle Silk	5.5	Yes	230–260	N/A	Superficial
Radiesse	N/A	No	1407	349,830	Medium-deep
Radiesse(+)	N/A	Yes	1180	310,000	Medium-deep
Restylane	20	No	514	119,180	Superficial-medium
Restylane-L	20	Yes	565	131,310	Superficial-medium
Restylane Silk	20	Yes	459	107	Superficial-medium
Restylane Lyft	20	Yes	549	127,090	Medium-deep

Adapted from Wilson AJ, Taglienti AJ, Chang CS, et al. Current applications of facial volumization with fillers. *Plast Reconstr Surg* 2016;137(5):873e; with permission.

agents that are currently used include butanediol diglycidyl ether, divinyl sulfone, biscarbodiimide, and 1,2,7,8-diepoxyoctane. Unfortunately, these cross-linking agents can be irritating and toxic to the skin; thus, all residues must be removed during the manufacturing process [15]. The manufacturing process enables HA fillers to be stored at room temperature with a defined expiration date.

Clinical indications for HA fillers are vast, and different HA fillers can be used successfully to rejuvenate all aspects of the aging face by the well-educated injector. In the United States, HA fillers have been Food and Drug Administration (FDA) approved for specific anatomic indications, but in practice they are often used off-label for optimal results. When selecting an HA filler, the differences in rheologic properties in relation to the anatomic qualities of the facial area to be treated should be considered. In general, HA fillers last approximately 6 months to more than 12 months, but a particular filler's longevity depends on multiple factors, including a patient's anatomy and metabolism, the specific filler properties, and the anatomic area injected. One of the main reasons why HA fillers remain the most popular globally is because of their low adverse effect profile and reversibility. Temporary pain, swelling, erythema, and bruising can occur postinjection, but these occurrences reflect side effects that can occur after any injection. The most common adverse effect is the development of a hypersensitivity reaction, occurring in 1/5000 patients, and, less frequently, infection, granuloma formation, and intravascular injection. The Tyndall effect occurs when an HA filler is injected too superficially causing a bluish discoloration in the skin. The ability to inject hyaluronidase in the treatment area to dissolve an HA filler and reverse most adverse events makes HA fillers the preferred soft tissue filler for injectors and patients alike.

Bovine Collagen

Bovine collagen (Zyderm and Zyplast) was the first dermal filler to be FDA approved for soft tissue augmentation and represented the gold standard filler prior to the introduction of HA fillers. Because of the risk of hypersensitivity to bovine collagen and subsequent need for preinjection skin testing, however, coupled with its short duration of effect, bovine collagen's popularity rapidly declined.

Human Collagen

Human collagen fillers were introduced as an alternative to bovine collagen that had the benefit of a lower risk of hypersensitivity reaction formation. These fillers were composed of bioengineered human dermal tissue

designed to replace lost collagen with a similar 3-D scaffold that would allow ingrowth of native dermal fibroblasts. Because of its short duration of effect and limited applications, however, human collagen's popularity rapidly declined after the introduction of HA fillers.

TYPES OF SYNTHETIC FILLERS

Calcium Hydroxylapatite

CaHA (Radiesse) is a semipermanent filler manufactured and distributed by BioForm Medical (San Mateo, California). CaHA is a suspension of 30% CaHA microspheres 25 μm to 45 μm in diameter in a 70% gel composed of 1.3% sodium carboxymethyl cellulose, 6.4% glycerin, and 36.6% sterile water. The CaHA microspheres form a scaffold for the ingrowth of fibroblasts and resultant production of new collagen. The microspheres are immunologically inert and do not stimulate a foreign body reaction. As such, only fibrin and scant cellular tissue are formed around the microspheres. Beginning at approximately 9 months, the microspheres begin to become adsorbed because of enzymatic breakdown into calcium and phosphate.

CaHA can be stored at room temperature and, like HA fillers, may be mixed with lidocaine prior to injection. Because of the size of the microspheres, a long, large, 26-gauge or larger needle should be used for injection and should be injected deep to the dermis to avoid visible material and product palpability. In 2006, CaHA was FDA approved for oromaxillofacial defects, facial wrinkles and folds, and lipodystrophy in HIV patients. In clinical practice, CaHA is an excellent choice for correcting deep volume loss in the upper, mid, and lower face and has been used safely in dorsal hand volumization [14]. In particular, CaHA has been shown superior to collagen and several HA fillers for treating the nasolabial folds (NLFs) [16–18]. Although results vary, the effects of CaHA have been reported to persist for 9 months to 18 months [7,19]. Aside from the typical temporary adverse effects that occur with all fillers, there are no major systemic adverse effects of immunologic responses associated with CaHA. CaHA should not be injected into superficial areas, however, such as the lips because the activity of muscles, such as the orbicularis oris, facilitates easy degradation of methylcellulose and clumps together the microspheres as hard calcium nodules [20,21]. Furthermore, unlike HA fillers, CaHA cannot be directly enzymatically reversed postinjection, making it a less desirable filler for injectors and patients who wish to have the flexibility and safety of reversibility.

Poly-L-Lactic Acid

PLLA (Sculptra) is another semipermanent filler, considered a biostimulator, that is manufactured in Italy and distributed by Dermik Laboratories (Berwyn, Pennsylvania), a division of Sanofi-Aventis (Bridge-water, New Jersey). PLLA is supplied as a powder of PLLA microspheres 40 μm to 63 μm in diameter, sodium carboxymethylcellulose, and nonpyrogenic mannitol. This powder must be hydrated with sterile water to create a hydrogel with a methylcellulose carrier prior to injection. The PLLA microspheres are believed to gradually be metabolized to CO_2 and water. This causes a foreign body reaction and activation of dermal fibroblasts to enable ingrowth of type I collagen. It is a delayed process, so the overall clinical effect may require multiple treatments to manifest but effects can last upwards of 2 years with continued treatment [22].

The freeze-dried PLLA powder can be stored at room temperature up to 30°C. The powder within a given vial is reconstituted with a minimum of 5 mL (typically 9 mL) of sterile water or 4 mL of sterile water and 1 mL of 2% lidocaine, depending on injector preference and injection site. PLLA may be injected 2 hours after reconstitution, but longer hydration time of more than 48 hours has been demonstrated to reduce the incidence of nodule formation [23,24]. A minimum of a 26-gauge needle should be used to inject the product deep to the dermis, into the subcutaneous or supraperiosteal space. Most patients require a series of 3 to 4 injections spaced 2 weeks to 6 weeks apart for sufficient pan facial volumization [25,26]. To ensure proper dispersion to avoid nodule formation, patients are typically instructed to massage the injected regions for 5 minutes, 5 times a day, for 5 days, although there is little evidence to suggest this is necessary when using larger and longer reconstitution parameters.

PLLA initially received FDA approval for the treatment of lipoatrophy of the cheeks and temples for HIV patients in 2004 and was later approved for aesthetic volumization of the aging face in 2009. The most common adverse effects are localized ecchymosis and edema, but PLLA can cause subcutaneous papules and granulomas, which can be minimized with increased reconstitution volume time and patient massage [25,27]. PLLA is not as effective or safe when injected intradermally or subdermally in areas with hyperdynamic musculature, such as the glabella, crow's feet, oral commissures, and perioral regions [24]. Like CaHA, PLLA cannot be directly enzymatically reversed postinjection, and severe nodules may require surgical dissolution or excision. Because of PLLA's unique

properties in delayed biostimulation rather than immediate tissue filling, its application is not discussed further in this article.

Polymethylmethacrylate

PMMA (Bellafill) is the most commonly used permanent filler and is manufactured and distributed by Suneva Medical (Santa Barbara, CA). PMMA is a homogenous solution of 20% PMMA microspheres 30 μm to 50 μm in diameter evenly suspended in partly denatured 3.5% bovine collagen and 0.3% lidocaine. The microspheres of PMMA are considered permanent because their size, smooth surface, and lack of electrical charge, enabling them to resist phagocytosis and dislocation as they are encapsulated by endogenous collagen [7]. The bovine collagen is completely resorbed by 3 months and is replaced with human collagen [7].

PMMA should be stored at 2°C to 10°C and warmed to room temperature before use. All patients should be skin tested 1 month prior to injection for allergy to the bovine collagen component. A large 26-gauge needle should be used for injection to accommodate the sphere size. PMMA is best injected into the deep dermis or immediate subdermis to avoid nodule formation. It was FDA approved for treatment of the NLFs in 2006 and subsequently for acne scars in 2015. The most common adverse effect is lumpiness, but other complications include allergy to the bovine collagen component, hypertrophic scarring, and granuloma formation. Finally, unlike HA fillers, PMMA is considered largely permanent and cannot be directly enzymatically reversed postinjection, making it a less desirable filler for injectors and patients who wish to have the flexibility and safety of reversibility. Because of PMMA's unique permanent properties and its current small market share in the United States, its application is not discussed further in this article.

Product Choice

Choosing which filler to use may seem like a daunting task given the many different properties and classifications and the continuous introduction of new products and technologies. In particular, for HA fillers, which are the most commonly used, it is important to consider the rheologic properties of a given filler and whether a filler with those specific characteristics can safely and successfully accomplish the clinical goals of the injector and patient. Furthermore, it should be considered that product properties can be altered via blending with normal saline or other mixing agents. Ultimately, product selection should be based on clinical experience and

comfort level. Excellent results can be achieved with a wide variety of fillers in multiple anatomic areas.

INJECTION TECHNIQUES AND GENERAL CONSIDERATIONS

Injection Techniques

Multiple injection techniques exist and are often used in combination with one another to achieve optimal results for a given anatomic region. The 4 most commonly used injection techniques are serial puncture, linear threading, fanning, and cross-hatching. Although each of these techniques may be better applied in certain indications, which technique should be used ultimately comes down to experience and comfort level because excellent results can be achieved with all.

The serial puncture technique involves multiple injections that are made serially, typically perpendicular to the skin, along a fine wrinkle or fold. The injection sites should be close together so that the filler merges into a smooth, continuous line that lifts the wrinkle or fold. The filler may be massaged after injection to eliminate any gaps and to achieve a smooth result. This technique is best performed by pulling the skin slightly away and out from the injection area. Serial puncture is most effective for superficial injections to correct fine wrinkles, such as the glabella, philtral columns, NLFs, and other fine rhytides.

The linear threading technique involves uniform deposition of the filler as the needle is slowly advanced (anterograde) or withdrawn (retrograde) from the tissue through a single or a few injection points, parallel to the treatment area. This technique is most commonly applied to the NLFs, glabella, and lips.

The fanning technique is similar to the linear threading technique in that it reflects multiple threads oriented in a fanlike manner. The fanning pattern of lines should be evenly spaced in a clockwise or counterclockwise direction to address the desired treatment area. Fanning is effective at distributing filler over a wide distance, such as the malar region, or can be used in a more defined area such as the lip.

The cross-hatching technique involves multiple linear threading injections in the horizontal and vertical directions to form an evenly-spaced grid. It is important to demarcate the injection lines prior to injecting to achieve optimal results. Cross-hatching is effective at distributing filler over a wide region, such as the malars, or more defined areas, such as the oral commissures.

Other techniques that may be used, particularly for filling of deep folds or rhytides, such as the malars, temples, or jawline, are towering, layering, and depot

injections. Regardless of which technique is used, aspirating should be considered prior to product injection to minimize the risk of intravascular injections.

Blunt Cannula Versus Fine Needle

Filler injections were initially performed with fine needles, but as techniques expanded and became more sophisticated, more practitioners have been using a blunt cannula instead of a sharp needle for product injection. Because of the blunt tip, it is considered that cannula injection techniques may result in less tissue trauma. This can translate to increased patient comfort, reduced pain, edema, and bruising [28]. Furthermore, because it is more difficult to penetrate a vessel using a cannula, the risk of intravascular injection is believed lower with a blunt cannula technique. Despite these potential advantages, cannula use requires additional cost and training and thus its adoption has been more limited than initially predicted. Furthermore, many practitioners consider that there is increased precision with product placement via needle injection and therefore have shunned the use of the cannula technique. Additional time is required to determine whether cannulas will replace needles in the filler market.

Patient Preparation

To reduce the severity of postinjection bruising, patients should avoid taking aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants, if medically safe. Prior to injection, all makeup should be washed off. A 4% LMX topical anesthetic cream, or another topical anesthetic, can be applied prior to the procedure to improve patient comfort during injection. Alternatively, a local or regional anesthetic block may be performed. The skin is subsequently prepped with a topical antimicrobial. This is an increasingly important step because patients are receiving fillers more frequently and fillers are becoming longer lasting, thereby increasing the risk of bacterial colonization or infection. At the authors' institution, patients' skin is prepped with 70% isopropyl alcohol and then 4% chlorhexidine gluconate. After injection, patients may apply cold packs to the areas to improve comfort. Patient comfort and overall experience can be further improved by using fillers mixed with lidocaine. Although lidocaine was initially believed to potentially reduce the durability of the product and increase risk of allergy, fillers with lidocaine have been shown to have similar safety and effectiveness profiles as fillers without lidocaine. Finally, adjunct products, such as oral or topical arnica or other anti-inflammatory agents, may be supplied to optimize the patient experience.

REJUVENATION OF THE UPPER FACE

Age-Related Changes

The upper face is defined as the area from the glabella inferiorly to the hairline superiorly and includes the temples laterally. With advancing age, the forehead, temples, and lateral brow undergo thinning of the dermis and subcutaneous tissues while the muscles of the upper face can become hyperdynamic to accommodate these changes. This results in skin laxity, contour deformities, and dynamic rhytides of the forehead and glabella. The skin overlying the temples and forehead becomes thinner, making the underlying vasculature and bony structure visible and increasing the risk of visible lumps and irregularities from injected fillers. The deep temporal fat pad, the temporal extension of the buccal fat pad, and the temporalis muscle atrophy with age, resulting in hollowing of the temples. Furthermore, as the temples narrow, the lateral brow support loses its support, resulting in lateral brow ptosis and perceived loss of the lateral brow. Pseudodermatochalasis of the upper eyelid develops from loss of the central brow soft tissue support and creates a tired, aged appearance of the upper face as well as frontalis strain for compensation.

Temples

When rejuvenating the upper face in a patient with panfacial volume loss, including the temples, it is reasonable to consider injecting the temples first. Reconstitution of the depressed temple volume augments the lateral brow, potentially eliminating or minimizing the need for further volume restoration of the brow or related structures and results in a natural correction. To correct for the significant soft tissue loss and resultant depression of the temples that occur with age, a filler with a high G' and n^* , such as Restylane Lyft, Restylane-L (Galderma, Lausanne, Switzerland), Juvéderm Voluma XC (Allergan, Dublin, Ireland), or Radiesse, should be used, especially when injecting in the deep plane, such as the suprapariosteum. The filler can be serially injected in the suprapariosteal plane lateral to the temporal crest and at least 1 cm away from the brow using a perpendicular depot technique. To facilitate injection in the proper deep planes while avoiding superficial temporal vessels, the skin should be spread to tented up prior to needle insertion. If a patient has depressions extending into the supraorbital area, injecting using a linear threading technique can be done along the medial temples in the same plane. If a patient has thin skin, the HA or Radiesse filler can be diluted with normal saline to decrease the risk of visible lumps or irregularities. Although the suprapariosteal plane is the safest plane of injection from a vascular

standpoint, it typically requires a high G' product and adequate volume to correction. Thus, some injectors prefer to inject in the subgaleal plane to minimize product use and cost to the patient. The major anatomic structures to avoid when injecting the temples are the superficial temporal vessels and associated superficial veins as well as the frontal branch of the facial nerve. Care should be taken to be in the correct plane to avoid the sentinel vein and to use a product that is adequately soft and smooth to prevent irregularities in this more superficial plane. Finally, the patient should be warned about the temporary venous congestion that often accompanies filler injection to this area.

Brows

As previously described, volume restoration of the temples can correct lateral brow ptosis. Thus, injecting the temples prior to direct manipulation of the brow position should be considered if both areas suffer from volume depletion. If the patient retains residual lateral brow ptosis after volume restoration of the temples, filler can be injected lateral to the brow and along the transition between the brow and bony orbital rim to achieve a confluent brow lift. Because volume loss occurs in both bone and the subcutaneous and retro-orbicularis fat, injection should be directly onto periosteum laterally and more superficial medially, to avoid the supraorbital and supratrochlear neurovascular structures. This dual volumization requires a filler with a reasonably high G' and n^* and low diffusion capacity, such as Restylane Lyft, Restylane-L, Juvéderm Voluma XC, or Juvéderm Ultra Plus XC.

Forehead

The horizontal rhytides of the forehead are primarily dynamic in nature and are best treated with neurotoxins. Dermal atrophy and general soft tissue volume loss, however, exacerbate the forehead rhytides at rest and with animation, and, if severe enough, neuromodulation may not sufficiently efface static rhytids alone. The combination of a neurotoxin and a filler with a low G' and n^* and moderate xStrain properties can effectively rejuvenate the dynamic and static forehead. Such fillers include Restylane Defyne, Restylane Refyne, Restylane-Silk, Juvéderm Ultra Plus XC, and Juvéderm Ultra XC. To facilitate even spreading along the rhytides, a serial puncture or linear threading technique should be used, and the filler may be layered to fill deeper rhytides. Reducing the severity of the forehead rhytides is best accomplished with superficial injections either at the epidermal-dermal border or intradermally. This further avoids intravascular injection into the

supraorbital and supratrochlear vessels and spread of the product in the suprapariosteal plane.

Glabella

The etiology and management of glabellar rhytides are similar to those of forehead rhytides but pose more risk from the proximity to the supraorbital and supratrochlear and associated neurovascular structures. A combination approach using both neurotoxins and fillers is the most effective means of reducing the severity of dynamic and static rhytides of this region. Fillers with a moderate G' and n^* , and low xStrain, such as Restylane-L, Restylane Silk, Belotero Balance (Merz, Frankfurt, Germany), and Juvéderm Ultra XC, are effective for this region. Regardless of the depth of the rhytides, a serial puncture or linear threading technique is effective for this region of the upper face. Finer etched-in lines should be injected in the epidermal-dermal junction, whereas deeper and wider folds should be injected intradermally. It is critical that all filler injections be performed superficially and conservatively in this region to avoid catastrophic vascular complications.

REJUVENATION OF THE MIDFACE

Age-Related Changes

The midface is defined as the area from the subnasale inferiorly to the glabella superiorly and extends laterally to include the entire height of the ears. Multiple bony and soft tissue changes occur in the midface and associated periorbital region. Remodeling of the periorbital bones in the superomedial and inferolateral direction vertically lengthens orbital aperture with an increased susceptibility to lower lid hollowing and contour deformities.

Furthermore, atrophy of the inferior lid fat compartments, suborbicularis oculi fat, laxity of the orbicularis oculi, and orbitomalar ligament widen the lateral canthal angle by putting inferior strain on the lower lid. There is also descent of the lateral canthal tendon, loss of the lower eyelid tone, and hollowing, resulting in the characteristic tear trough deformity and lower eyelid bags. These age-associated soft tissue changes are further exacerbated by bony shifts manifested as maxillary retrusion in a superior and posterior direction as well as posterior rotation of the maxilla. This leads to a loss of malar projection, otherwise known as a negative vector, along with loss of nasal support accentuating the loss of lower eyelid contour in combination with a decrease in the maxillary angle and a widening and deepening of the pyriform aperture.

These complex soft tissue and bony changes together contribute to the deepening and involution of the characteristic NLF.

Malar Region

Precise restoration of midface volume loss can rejuvenate both the upper and lower face. The malar region is the key foundation of the midface. With the largest width on the face usually found at the bizygomatic distance, the zygomatic arch provides the foundation for the periorbital area superiorly and the perioral area inferiorly. Thus, malar volume loss should be first corrected when age-related changes affect all of these regions. This concept cannot be overemphasized in patients whose malar volume loss contributes to NLF severity and the tear trough deformity. The exception is a patient who presents early in the aging process with isolated NLF rhytides or nasojugal grooves, without discernible malar volume loss. Juvéderm Voluma XC and Restylane Lyft are currently FDA approved for the malar region, but any filler with a high G' and n^* , such as Restylane Defyne, Restylane-L, Radiesse, and Juvéderm Ultra Plus XC, can effectively provide deep volumization to the malars.

Most commonly in the malar region, a high G' product is injected in the suprapariosteal plane or under the malar fat pad using a depot, stacking, or towering technique to lift and accent the most prominent portion of the malar eminence in relation to patients' ethnicity and anatomy. The goal of malar augmentation is to restore the original volume and proportions with the lateral malar and zygomatic areas comprising the widest portion of the face. Creases or depressions between fat pads should further be minimized, because submalar hollowing contributes to a gaunt, worn-out look of the aging face. To treat submalar hollowing or to treat thin patients, injection can be subcutaneous or into the deep or superficial fat pockets to achieve a more neutral or minimally concave contour. Fillers, such as Restylane Defyne and Juvéderm UltraPlus XC, that possess a more moderate G' and high xStrain are best suited for this region to maintain a natural appearance. Most patients do not desire a convex contour of the anterior or submalar region, because this approach can create an unnaturally full appearance. For patients who desire a youthful baby face, it is preferred to inject around the malar area as opposed to projecting the submalar area. The major anatomic structure to avoid in this region is the infraorbital neurovascular bundle when injecting the anteromedial malar compartment. Thus, injections to this region should be made superficial to the suprapariosteal plane.

Superior Periorbital Area

Rejuvenation of the superior periorbital area and upper lid aims to further boost the lateral brow and volumize medial and central upper lid hollowing. This region is best injected superficially with a filler with a low G' and n^* , and moderate xStrain, such as Restylane Refyne, Restylane Defyne, Belotero Balance, or Juvederm Ultra XC. Superficial injections using a linear threading technique with postinjection massage and/or blending with normal saline can achieve excellent results. Direct suborbicularis injection to the upper lid may better be able to correct upper lid hollowing, but because of the close proximity of the globe of the eye and its vasculature, this technique should only be used by expert injectors highly familiar with this anatomy and the differential properties of fillers.

Inferior Periorbital Area

The goals of rejuvenating the inferior periorbital area include contouring the medial and lateral orbital rims, correcting the tear trough deformity, and restoring the youthful lower lid to cheek transition. Fillers with a low G' and n^* , and low hydrophilicity, such as Restylane Refyne, Restylane Silk, and Belotero Balance, are best for this area, which is comprised of extremely fine and malleable tissues prone to edematous changes secondary to lymphatic drainage dysfunction. In this region, more than others in the face, it is critical to accurately assess the quality of tissues for proper product selection. Patients with poor tone in this area may only tolerate the softest, lowest G' products, or they may not be filler candidates at all. Those with adequate tone can typically be treated with the fillers described previously. Hydrophilic products should be avoided in this region, because they can predispose patients to unpredictable edema formation.

Contour deformities of the medial or lateral orbital rims may be corrected after injection of the malars, if indicated, with conservative linear threading in the suprapariosteal plane. When injecting this area, it is important to aspirate prior to injecting or to consider using a blunt cannula to avoid intravascular injection that could lead to retinal artery occlusion and blindness. Slow under-correction is key. Patients should typically not receive more than 1 mL of product to the tear troughs at any given time. If additional correction is required, this should be completed in a staged fashion. The tear trough deformity is not a feature of the youthful face, so effacing this deformity should be attempted, to restore a youthful, rested appearance. Treating the tear trough deformity is best performed with serial and linear threading from a lateral to medial direction

in the suprapariosteal plane, followed by product massage to prevent contour deformities. It is important to avoid injecting into the angular artery that resides near the apex of the medial canthus. Finally, the smooth transition from the lower lid to cheek characteristic of the youthful face can be restored with suborbicularis threading of very small amounts of filler. This helps improve creasing of the preseptal lid or at the junction of the preseptal and pretarsal portions of the lid and can be combined with conservative neuromodulation of this region.

Crow's Feet

The crow's feet deformity appears and worsens with age as the orbicularis oculi muscle becomes hyperdynamic and the dermis and subdermis thins. The crow's feet are best treated via neuromodulation initially, a treatment that often requires a filler for the remaining deepening static rhytides with advancing age. To minimize contour deformities, edema, and ecchymosis, the ideal filler for this area should have a low G' , n^* , and hydrophilicity. These include Restylane Defyne, Restylane Refyne, Restylane Silk, Juvederm Ultra XC, and Belotero Balance. Injection should be in the deep dermal plane using a serial puncture, threading, or cross-hatching technique depending on rhytid presentation. Products may be blended with saline and massaged to minimize contour irregularities.

Nasolabial Fold

Treatment of the deepening and involuting NLF, despite its treatment longevity, remains controversial. Unlike the rest of the face, the NLF hypertrophies with age, resulting in a deeper fold that can become involuted in certain patients. It should be recognized, that unlike many features of facial aging, the NLF is a normal facial feature in youth and should not be completely effaced or have a convex contour. Thus, the goal of NLF treatment is to soften its appearance in a synergistic manner to the rest of the face. A recent school of thought believes that fillers are used incorrectly to volumize the NLF and should instead be first used to correct other midface deficiencies that contribute to the NLF. Conservative NLF injection to soften a residual prominent fold can then be treated secondarily.

In contrast, other injectors continue to advocate for deep volumization of the NLF with a high G' and n^* filler at the dermal-subcutaneous junction, followed by superficial dermal injection to correct residual fine rhytides. The fillers may be selected to have high to low xStrain depending on patient anatomy. To fill the fold, an inferiorly based fanning technique and

injecting in a retrograde fashion superomedially toward the base of the nose can be used. Any residual superior NLF depth can be filled using a serial puncture, linear threading, or cross-hatching technique oriented superomedially to inferomedially in a retrograde fashion. Irrespective of the technique used, correction should be aimed at or medial to the NLF and injection of product lateral to the fold should be avoided, because this may worsen the defect. Finally, this commonly injected region is also one of great vascular danger secondary to its proximity to the facial artery that traverses the subcutaneous tissues in a superomedial fashion close to the fold. Therefore, injections to this region should be superficial to the subcutaneous tissues to avoid vascular compromise.

Nose

Aesthetic deformities of the nasal dorsum or tip can be corrected with conservative amounts of fillers. Small amounts of a high G' and n^* and low xStrain filler can be injected in short linear threads or via serial puncture into the supraperiosteal plane superficially or suprachondrial plane inferiorly. Extra caution must be taken when injecting filler into the nose given the tight skin envelope and vascular anatomy requiring that injections be limited to the nasal midline to minimize the risk of intravascular injection to the angular artery and its branches, which can result in local or distal tissue necrosis, blindness, or even an occlusive stroke. Finally, only conservative amounts of filler should be injected in a staged fashion to avoid pressure-induced soft tissue necrosis.

Maxilla and Alar Base

Volumization of the maxilla can rejuvenate surrounding facial structures and avoid unnecessary excess filling of the NLFs and other related regions. For example, deep volumization at the level of the nasal sill and alar base can support the nasal tip, help correct the upper NLF, and lift the upper lip. The best fillers for this region are large-particle fillers with a high G' , such as Restylane Lyft and Voluma XC. The needle should be directed at the lateral most point of the alar base and advanced down to the periosteum, superior to the dentition and deep to the oral mucosa. The product should be placed as serial depots.

REJUVENATION OF THE LOWER FACE

Age-Related Changes

The lower face is defined as the area from the subnasale superiorly to the menton inferiorly and extending

laterally to include the body and angle of the mandible. Multiple soft tissue and bony changes occur in both the jawline and the perioral region with advancing age. Bony atrophy of the jaw, progressive descent and loss of fat pads, increased septal laxity, perioral muscle hyperactivity, and loss of skin elasticity contribute to the formation of perioral rhytids, down-turning of the lips, the formation of jowls, and the diminution of jaw contour. The age-related changes of the jowl are exacerbated by volume loss in the region anterior to the jowls, the prejowl sulcus, and volume loss posterior to the masseter in the posterior jawline and inferior preauricular region. Furthermore, bony loss contributes to the appearance of a depression or notch between the jowl and the bony mentum with an overlying descending fat pad, which manifests as the prejowl sulcus. The perioral region undergoes both superficial and deep atrophy. This manifests as lengthening and flattening of the upper lip complex and loss of vermillion and the formation of fine or deep vertical perioral rhytides. The oral commissures turn downward as opposed to upward in the youthful face. The mentalis region flattens and becomes ptotic. These superficial soft tissue changes are superimposed and intensified by changes to the mandible. There is a decrease in vertical ramus height, widening of the mandibular angle, and loss of anterior mandibular projection. These multifaceted interrelated changes underscore the complexity of facial filler treatment of the lower face.

Perioral Region

Restoration of the perioral region includes treatment of the upper and lower cutaneous lip, the oral commissures, and the lip itself. The goal of perioral volumization is to restore and support the entire lip complex. Treatment of the cutaneous lip and oral commissures, when indicated, should ideally be performed prior to direct (mucosal) lip augmentation. The oral commissures should be injected in the subcutaneous plane using a depot and linear threading technique until a subtle upturning is achieved. Restoration of the normal upturning of oral commissures can be facilitated by the addition of neurotoxin treatment of the depressor anguli oris muscles. The upper and lower cutaneous lip can be supported via volumization of the subcutaneous plane external to the white roll, which not only improves the appearance of the vertical rhytides but also restores the age-related atrophy of the subcutaneous plane responsible for these rhytids and the in-turning and lengthening of the upper lip. Conservative injection of neurotoxins into the upper and lower orbicularis oris muscle can further assist in improving the appearance

of the vertical rhytides of the upper cutaneous lip. Fillers along the entire spectrum of rheological properties may be used in the perioral region and should be selected to match a patient's tissue quality and severity of deficiency.

Lips

The goal of lip rejuvenation is to restore or accentuate the natural ideal contours of the lip, reflate the lip to treat age-related vermillion creasing and involution, and correct rhytides extending into the white roll. This should be accomplished by accentuating each of the natural components of an ideal lip. Injection may be in the white roll conservatively to highlight the outline of the lips or in the vermillion-cutaneous junction to volumize the mucosal lip. The vermillion should be enhanced only to the extent to fill the deflated contour of the lips, avoiding unnatural over-projection. Selection of fillers for lip injections should be based on the goal of the treatment and can include products along a spectrum of rheological properties. Under-correction is recommended due to the likelihood of swelling and for cases requiring more aggressive treatment, a staged approach is recommended. Radiesse should not be used in the lip because of its opacity, texture, and inability for dissolution. Furthermore, rejuvenating the entire perioral region can help to restore the youthful appearance of the lips. For example, augmentation of the philtral columns can enrich lip augmentation and perioral injection of neurotoxins may help increase the longevity of lip fillers.

Jawline

Soft tissue loss and migration over the mandible creates an indistinct border of the jaw and diminished facial width, resulting in an aged appearance. The goal of jawline rejuvenation is to contour the shape of the mandible to project anteriorly, laterally, and superiorly into the surrounding tissues while leaving a sharply defined edge inferiorly. Injection along the mandibular border is best performed in the supraperiosteal plane using a depot or cross-hatching technique with a 2-cm area of overlap at the angle of the mandible. Injection of the preauricular region is best performed in the subcutaneous plane using a threading technique. Some patients present with depressions along the body of the mandible posterior to the jowl and can be treated with linear threading. It is important to not overfill the anterior jawline when injecting women because it gives the appearance of a masculine square jaw. There are several anatomic structures that must be avoided when injecting along the jawline, namely: the parotid gland, the marginal mandibular and mental nerves,

and facial vessels. Fillers for this region should be selected based on whether the goal is to lift and restore structure, requiring a high G' product, or more superficially volumize, in which case a product with higher flexibility is indicated.

Jowls

Although moderate to severe jowls are best treated with facial rejuvenation surgery, fillers can be used to neutralize mild jowls and create a more aesthetically pleasing transition from the angle of the mandible to the menton. Along the jawline, filler can be injected in small depots deep under the soft tissues in the supra-periosteal plane or in a deep to superficial column to raise the surface contour. The prejowl sulcus should also be injected to camouflage the depression between the jowl and menton. This can be accomplished by injecting in the deep dermal or dermal-subcutaneous planes using a fanning or cross-hatching technique until there is a smooth ramp between the jowl and menton. As for the entire jawline, fillers for treating this region should be selected based on whether the goal is to lift and restore structure, requiring a high G' product, or more superficially volumize, in which case a product with higher flexibility is indicated.

Marionette Lines

The marionette lines are a characteristic feature of the aging face and a frequent patient concern. Although complete effacement is the goal, it is difficult to achieve this in more severe cases due to the presence of the fibrous septae that divide the fat compartments and dermal attachments to the muscular fascia in this region. The folds can be directly filled in a deep plane using a cross-hatching, or depot technique, with a high G' product, and remaining rhytids can be corrected with a linear threading or serial puncture technique in the intradermal plane using a higher xStrain product. Under-correction is recommended in patients with severe atrophy of this region to avoid an unnatural flattening and squaring of the anterior jaw.

OTHER APPLICATIONS OF INJECTABLE FILLERS

Hand

With increasing age, the dorsum of the hand undergoes volume loss in between the metacarpals, leading to increased visibility of the veins and tendons in combination with superficial skin aging. Radiesse is an excellent choice to correct this volume loss because its white

color provides a concealing effect over veins and tendons. HA fillers can also be successfully applied to this region. When injecting, it is important to tent up the skin to avoid the tendon sheaths and the superficial veins.

Acne and Other Scars

Acne and other scars can be treated effectively with intradermal injection or subcision by sweeping the bevel of a needle beneath the scar to release the dermis. A variety of nonpermanent or permanent fillers may be used in this application.

GENDER-SPECIFIC CONSIDERATIONS IN MEN

Although a vast majority of patients seeking facial rejuvenation are women, men similarly experience bony and soft tissue changes that contribute to an aged appearance. Furthermore, men are increasingly pursuing aesthetic facial rejuvenation. Although most techniques used in women can be extrapolated to men, it is important to keep in mind the normal gender-specific anatomic differences when injecting fillers in for a masculine appearance.

In the upper face, the male eyebrows are flatter in contour and run horizontally along the orbital rim. In contrast, the female eyebrow is angular and peaks approximately 0.5 cm to 1 cm above the orbital rim. Men are particularly prone to orbital hollowing and the tear trough deformity because men tend to have more frontal bossing of the forehead and a prominent supraorbital ridge as well as a negative vector. Furthermore, hypertrophy of the orbicularis oculi pars palpebralis is more common in men, contributing to the bags under the eyes appearance. It is important to remember these anatomic differences when male patients present for upper face volumization.

In the midface, the key difference is that women have more projected and rounded cheekbones, whereas male cheeks are less projected and less full. Although male cheeks also deflate and rotate inferomedially, it is important to not over-inject and create feminine-appearing cheeks. Injections of the malar region in men should be more anteriorly oriented than those in women.

In the lower face, the male jawline is squarer, and strong projection of the mandible is masculine and desirable in men, unlike in women. Men also desire chin projection, so paying extra attention to filling the chin may improve a male's aesthetic result.

COMPLICATIONS AND HOW TO AVOID THEM

Adverse Effects

The most common adverse effects after filler injections are swelling, redness, bruising, and pain secondary to tissue trauma. The degree of adverse effects depends on filler type, amount of injected volume, and anatomic location. These adverse effects can be lessened by precise slow injection and by instructing patients to apply cold packs and pressure after treatment and avoiding strenuous exercise for 24 hours. Clinical judgment should be exercised regarding advising patients to temporarily discontinue immunomodulators, anticoagulants, and other drugs with anticoagulant properties to minimize bruising and bleeding. Adverse effects are more common in sensitive areas of the face, such as the tear troughs and lips.

Immediate Complications

Immediate complications are defined as those that occur within 2 days of injection. The most serious complications are secondary to vascular compromise, from intravascular injection of filler. Arterial injection manifests as immediate pain, skin blanching, and skin coolness, but the most pressing concern is potential permanent blindness from injection into the superior facial vessels, such as the supratrochlear artery, which anastomose with the ophthalmic artery. Venous injection manifests as slowly worsening pain and swelling. The affected area develops a purplish hue. If a patient develops signs of vascular compromise, injections should be stopped immediately and aspirating any product attempted. If using an HA filler, begin administering hyaluronidase immediately. The consensus recommendation is 200 U to 300 U of hyaluronidase spread over the entire area of impending necrosis and repeated frequently for at least 2 days [29]. Larger doses, 500 U to 1500 U, may be used if necessary, and hourly hyaluronidase injections continued until signs of tissue compromise improve [29]. Additional measures include topical nitropaste, warm compresses and massage, steroids, aspirin, heparin, hyperbaric oxygen, and intravenous prostaglandins [29]. To avoid intravascular injection, the large vessels near the injection points, aspirate prior to injecting, and use a blunt cannula if possible. The most commonly reported area of complication is the glabellar region. Also important is mindfulness of alar and nasal tip necrosis as a possible complication when injecting the NLF. Because venous injection is often due to overfilling, be sure to inject slowly with minimal pressure in small volumes at different points. If the orbit is

involved, immediate consultation with an ophthalmologist is required.

The Tyndall effect, most commonly associated with HA, should be considered. When placed too superficially and in excessive amount, a bluish discoloration is noted. This bluish is caused by blue light scattered much more than the other wavelengths by particles. The Tyndall effect is readily reversed with hyaluronidase.

As such, proper techniques, such as intermittent aspiration and cannulation, combined with intimate 3-D knowledge of the anatomy of vessels, are prudent to avoid such complications.

Early Complications

Early complications are those that occur 3 days to 14 days after injection and are typically due to filler-based reactions and inflammation.

For up to 2 weeks after injection, it is common and normal for patients to feel nodularity in the injected area. If the nodularity persists beyond 2 weeks, it is considered a late complication. Similarly, swelling that occurs during injection can result in asymmetry during this time period, but it is best to wait at least 1 month as for this to settle. Any inappropriate placement of product can be treated with needle aspiration, or if serious, incision and evacuation. If using an HA filler, hyaluronidase should be injected: depending on filler cross-linking qualities, a single injection of 10 U to 20 U for an area less than 2.5 mm or 2 to 4 injections of 10 U to 20 U for an area between 2.5 mm and 1 cm [29]. The more cross-linked fillers require higher doses for dissolution.

Allergic reactions may occur in up to 3% of patients treated with Bellafill because of the bovine collagen component. They are otherwise rare with the HA fillers, Radiesse and Sculptra [3]. All patients receiving Bellafill should be skin tested for allergy to bovine collagen 1 month prior to injecting.

The other major early complication is infection, both bacterial from skin flora and reactivation of latent HSV. If a patient has a history of HSV infection of the lips, treat prophylactically with acyclovir or valacyclovir. To prevent bacterial infection, have patients wash off makeup and prepare the skin with a combination of 70% isopropyl alcohol and 4% chlorhexadine gluconate. If a patient is showing signs of infection, defer the elective procedure until infection has resolved.

Late Complications

Late complications are those that occur more than 14 days after injection and are due to the body's immune reaction to the filler.

Although nodularity is common and normal for up to 2 weeks postinjection, any nodules that persist beyond 2 weeks are classified as late complications. There are 2 types of nodules: noninflammatory nodules that typically lack pain, erythema, and drainage, and inflammatory or infectious nodules that present with pain, erythema, and drainage. Noninflammatory nodules may be gently massaged or dissolved with hyaluronidase, if from an HA filler, or intralesional steroids. Inflammatory or infectious nodules should be cultured and treated with antibiotics covering methicillin-resistant *Staphylococcus aureus* for 4 weeks to 6 weeks and oral steroids. Dissolving the filler hastens infection resolution. Patients who develop nodules have been reported to be at increased risk of biofilm formation and should be treated carefully during subsequent injections [30–34]. If the nodules persist, they can be surgically excised.

Granulomas may occur in up to 1% of patients and typically appear between 6 months to 24 months after injection. These foreign body granulomas typically appear at all injected sites at around the same time and can grow rapidly. Intralesional steroids are effective in treating PLLA and PMMA. The steroid may need to be repeated if redness or granuloma persist at 3 weeks to 4 weeks [3]. Unfortunately, they are usually not as effective with CaHA. A potential complication of repeated intralesional steroids is skin atrophy, so other options include triamcinolone, betamethasone, and 5-fluorouracil [3]. If the granulomas persist, they can be surgically excised.

Other late complications that may occur are hypertrophic scarring and dermal ridges, which occur if filler is injected too superficially. These may be corrected with dermabrasion or surgical shaving. Lipoatrophy similar to that seen in HIV patients on highly active antiretroviral therapy can also occur [3,35,36].

SUMMARY

Treating facial aging continues to be a challenge for cosmetic surgeons and aesthetic physicians, but increased knowledge of the anatomic changes that occur with age and improved tools for rejuvenation enable achieving excellent aesthetic results in a minimally invasive way. Although fat grafting will continue to have its role in certain situations, the aesthetic field is turning to increasingly to temporary fillers, in particular HA fillers, because of their ease of use, better predictability, and safety profile. Facial volumization should be performed deep to superficial and cephalad to caudad. The appropriate filler should be selected based on anatomic site, patient-specific goals and soft-tissue

dynamics, and the properties of the filler. The most important consideration, however, is injector comfort and experience. Although this article focuses on facial rejuvenation with soft tissue fillers, fillers are just 1 component of the armamentarium, and the best aesthetic results are achieved when selecting the appropriate combination of rejuvenating products and procedures.

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High-Volume Lipofilling/Fat Transfer. New Methods, Techniques, and Technologies. What Is the Science?

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KEYWORDS

• Lipofilling • Fat grafting • Buttock • Gluteal • Augmentation • Fat transfer

KEY POINTS

- High-volume lipofilling has become widely used for gluteal augmentation with high patient satisfaction rates and durable results.
- Intramuscular grafting has demonstrated survival of fat graft injected more rapidly and in larger aliquots than possible in the breast and face, allowing for lipofilling volumes of 1 L and above per side.
- Creating a frame for the buttocks by lipocontouring a patient's trunk, abdomen, hips, and legs is the only way to achieve truly excellent results—gluteal augmentation is only 1 part of a comprehensive plan.
- Patients must be counseled regarding the low but present risk of fat embolism or death in cases of high-volume gluteal lipofilling if graft placement into the muscle is planned, and the provider must always exercise great care with intramuscular graft placement.

INTRODUCTION

Advances in liposuction and grafting techniques and equipment have enabled transfer of larger volumes of fat autograft than ever before. High-volume lipofilling has been effective in primary augmentation as well as reconstruction scenarios in the breast [1,2] and has found a popular application in gluteal augmentation. Lipofilling presents an attractive option to patients because the downsides of implants are avoided, natural feel of the tissues is preserved, and the liposuction to harvest the fat improves the appearance of the donor areas. Although seemingly simple in concept, high-volume lipofilling has its own set of complexities and

pitfalls that must be accounted for to avoid complications and provide aesthetically pleasing results.

Lipofilling in the buttocks for augmentation and contouring is discussed later, because this is the more hotly discussed application of high-volume fat transfer at this time. Lipofilling for breast reconstruction and augmentation has several other complexities outside the scope of this text and is well described elsewhere [2,3].

Buttock augmentation, pioneered by Toledo [4], has gained great popularity in the United States in recent years, as evidenced by consumer online search patterns, putting it second only to breast augmentation [5].

Disclosure Statement: The authors have nothing to disclose.

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Unlike the breast, a large amount of graft can be transferred due to the large subcutaneous fat and gluteus maximus muscle recipient sites. Although it is often the focus of discussion, buttock augmentation should be part of a liposculpture plan that must address the abdomen, flanks, back, hips, and thighs. Sculpting the frame for the augmented buttock is a complex endeavor and only the basics are included. Excellent descriptions and videos are available on this topic, which extend beyond the scope of this article [6,7].

Fuller hips and buttocks have become more desirable recently, and patients are requesting dramatic augmentations. These requires intramuscular graft placement, because the subcutaneous tissues can only support a limited amount of graft. This is of crucial importance because there is a correlation between fat embolism in gluteal auto-augmentation cases and grafting in the deep muscular layers, and providers must be aware of these risks.

SURGICAL TECHNIQUE

- Patient evaluation and preoperative planning
 - Patients' expectations and concepts of ideal body shape vary—some may seek maximal projection and volume, whereas others may want to recreate their younger, athletic body contours. A patient's goals dictate the donor sites available and the contouring that needs to be done, the amount of harvested fat available, and the augmentation plan in relation to need for intramuscular grafting.
 - The lipocontouring plan must address the flanks, abdomen, and back to create a smooth transition from torso to buttock and hips. It is key to suction any excess superolaterally to the gluteus maximus projection—this avoids the appearance of squared-off buttocks superiorly.
 - A general guideline is to aim for a 0.60 to 0.65 waist-to-hip ratio on the anteroposterior (AP) view, 0.70 waist-to-hip ratio on the lateral view, and for the most projecting point of the buttocks to be at the midpoint of the curvature, with 50% of the volume above and below. A useful landmark for this level is the coccyx, which should align with the pubis and greater femoral trochanter to localize the vertical midpoint of the buttocks [8].
 - Preoperatively, mark the bony landmarks (anterior superior iliac spine [ASIS] and posterior superior iliac spine [PSIS]), iliac crest, greater trochanter, and pubic symphysis), any areas of adipose excess around the buttocks to be suctioned, the donor sites, and the intertrochanteric depression, if present.
- Preparation and patient positioning
 - Patient is prepped circumferentially with warmed betadine solution and then assisted to the operating room (OR) table, which is covered with a sterile drape and towel, used later to turn the patient. Arms and legs up to the knees are covered with sterile stockinettes after intravenous (IV) catheters, pulse oximetry monitors, and sequential compression devices are in place.
 - After induction of anesthesia, the liposuction is started in the supine position, then lateral decubitus position, prior to turning to prone for the bulk of the lipofilling. The patient can be partially turned to lateral decubitus again, if needed, to graft the lateral areas and the intertrochanteric depression, before being turned back to supine for extubation.
 - Liposuction and grafting access sites are repped after all position changes.
- Procedural approach
 - The overall procedure is divided into 3 components: tumescence and liposuction, fat graft processing, and fat graft injection.
 - Anesthesia and tumescence
 - Fat grafting to the buttocks can be performed under IV sedation, but providers first starting to incorporate it into their practice may prefer general anesthesia at the outset. Under general anesthesia, the tumescent solution may be formulated without lidocaine to avoid any risk of any lidocaine toxicity with no impact on postoperative pain [9].
 - Any lidocaine used should be under 45 mg/kg [10]. Epinephrine dose should not exceed 0.07 mg/kg or 10 mg total [11,12].
 - The authors prefer infiltrating to tumescence with warmed lactated Ringer solution and epinephrine 1:1,000,000 (1 ampule of epinephrine 1:1000 in 1 L of lactated Ringer solution) under general anesthesia.
 - Liposuction
 - Most of the liposuction is in the deep plane to evenly decrease the subcutaneous adipose layer, where aggressive cannula designs may be used per surgeon preference. For contouring the superficial layer over the anterior abdomen, a less aggressive design minimizes

contour deformity risk. Power-assisted liposuction can decrease surgeon fatigue and speed up the process, and an ultrasound-assisted handpiece can be effective in fibrous tissues

■ **Supine position**

- Stab incisions are placed low bilaterally in the suprapubic region and in the umbilicus for access. The anterior abdomen is uniformly suctioned in the deep (sub-Scarpa's fascia) plane via access incisions in the umbilicus and bilaterally in the suprapubic area. Targeted passes in the superficial fat layer define the lateral and medial edges of the rectus muscles (the linea alba and semilunaris bilaterally) as well as the horizontal inscriptions across the rectus. This etching creates an attractive, youthful abdomen.
- The anterior aspect of the fat pad superior to the iliac crest is addressed, although it is suctioned primarily in the lateral decubitus position. Avoid liposuction inferior to the iliac crest, because this can create a step-off.

■ **Lateral decubitus position**

- Incisions are placed medial to the ASIS, low in the underwear line, to suction the flank and the posterior triangle, hollowing out the area superior to the buttocks and hip in the AP view, decreasing the waist-to-hip ratio. A complementary incision at the superior end of the gluteal cleft is made to address the same area and the presacral fat from the posterior approach.
- While in lateral decubitus, the goal is to suction the fat superior to the iliac crest to sculpt the waist and create a smooth transition to the buttock posteriorly and the hips laterally. The superolateral quadrant of the buttocks is one of the key areas that must be addressed in this position—excess volume here makes the buttocks appear square.
- Using the towel placed on the OR table preoperatively, the patient is turned and the contralateral side is treated.

■ **Prone position**

- The gluteal cleft incision is the access point for the lower back and flanks, the posterior triangle, and any fullness in the area of the medial gluteal fold.

- Incisions are made over the PSIS bilaterally to approach these areas again with overlapping cannula trajectories.
- The V-shaped area over the sacrum must be treated aggressively from all 3 approaches. Along with liposuction of the lower back, it decreases the waist-to-hip ratio in the lateral view and creates the appearance of a more projecting buttock. Moreover, the depressed V-shape over the sacrum creates a rounded, diverging silhouette of the buttocks superiorly, much like the V-shaped cleavage produced by a push-up bra.

○ **Fat graft processing**

- The system below is just one of the many available options. Closed systems are more complex and expensive but may offer a lower contamination risk. Reported infection rates are low, however, with open systems [6,13].
- A simple and effective system uses a large (2-L) collection canister, which is autoclave-safe, placed on the sterile field to collect the lipoaspirate. Sterile vacuum tubing is connected to the canister and connected to the liposuction machine off the field, and the canister is connected to the cannula or powered handpiece with another sterile piece of tubing. In this fashion, the lipoaspirate never leaves the sterile field. Some canisters are available with a spout at the bottom to decant the liquid part of the supernatant prior to removing the fat for loading the grafting syringes. Otherwise, 2 canisters can be used, which are switched once full and the lipoaspirate is allowed to separate by gravity for 15 minutes to 30 minutes.
- An alternative is straining the fat, which is also a straightforward method that is well described [6,7].
- The fat graft is loaded into 10-mL or 60-mL syringes, per surgeon preference. The grafting cannula should be blunt-tipped and at least 3 mm in caliber (4 mm or larger if grafting the muscle).

○ **Fat graft injection—gluteal augmentation**

- The fat graft placement has 2 goals: increasing the perceived projection and volume of the gluteus maximus and the buttock overall and creating a smooth transition from the lower torso/waist to the buttocks/hips.

- The buttock is divided into 4 quadrants to visualize the areas with the most volume deficiency. The horizontal line is at the level of the coccyx/greater trochanter, and the vertical line is drawn at the midpoint of the buttock.
- The key to graft placement is the differentiation of volume versus contour. The superficial muscular layer is well vascularized and thus can accept a larger amount of graft per volume of recipient site compared with the fat layer. Being deeper, it has less effect on the buttock contour, so the intramuscular grafting is best for overall volume augmentation. The subcutaneous fat layer is also grafted for volume, but graft in this layer has greater power to shape the contour and smooth transitions. An analogy is that putting a golf ball under a blanket (in the subcutaneous fat) shows much more than putting one under a mattress (in the muscle).
- Intramuscular graft placement is done with constant caution and attention—the surgeon must visualize the path of the cannula at all times in his or her mind. The cannula trajectory should be parallel to the thigh or pointing superficially, never toward the OR table. Angled or curved cannulae can be useful in achieving this trajectory.
- The buttocks are grafted through incisions in the infragluteal crease and laterally. Fanning trajectories from these incisions allow even placement of graft through noncontacting tunnels in multiple layers. Care should be taken to ensure the graft is placed into discrete spaces and does not coalesce. The lateral gluteal area and intertrochanteric depression are filled first to round out the lateral buttock and hip. The buttock quadrants with deficient volume or projection are filled last.
- The intertrochanteric depression can extend from the lateral aspect over the gluteal muscle all the way anteriorly, and all these aspects must be addressed so that the hip and buttocks silhouette is smooth and round from all angles. The patient may need to be rolled into a partial decubitus position to gain access to the anterior aspects of the hip.
- Final touches
 - Once the fat graft is injected, overall volume and contour can be assessed. Depressions

are treated with more lipofilling or by passing an exploded-tip cannula with the suction off, as in the equalization portion of the separation, aspiration, and fatty equilibration (SAFE) liposuction protocol to redistribute the fat [14].

- A drain is recommended for the presacral space—a Penrose drain is usually sufficient and is easy to remove in the office at follow-up. A triangular bolster is also made at this time and placed over the sacrum once the garment is on.
- The access sites for the liposuction and fat graft placement may be left open to drain or closed with a simple suture, per surgeon preference. Jackson-Pratt drains may be placed in the lower abdominal access sites per surgeon judgment once the patient is turned supine.
- The patient is placed in the postoperative compression garment and woken from anesthesia. A triangular bolster is placed inside the garment to keep pressure over the sacrum. Similar bolsters or towels are placed over the posterior triangle, with the garment holding them in place.

REHABILITATION AND RECOVERY

- Postprocedural care
 - Drain care
 - Drains are removed once output is less than 30 mL/24 hours for the Jackson-Pratt drains or when no longer productive for the Penrose drain.
 - Garment
 - The garment should cover all the treated areas and be tight over the suctioned zones while minimizing the amount of compression over the buttocks where the fat graft was placed. It is worn for 4 weeks to 6 weeks, except for showering.
 - Hygiene
 - Patients shower at 1 day to 2 days postoperatively, with no submersion for 3 weeks.
 - Positioning
 - Immobilization and protection of the graft are key to maximum take.
 - The more aggressive postoperative protocol includes turning the patient prone in the post-anesthesia care unit once awake enough, and then transport home and for the next 1 week

to 2 weeks must be in the lateral decubitus or prone position. All pressure is kept off the buttocks for 6 weeks. After 10 days, patients may sit using a pillow or other bolster behind the upper thighs, so that the buttocks are not weight bearing.

- The postoperative protocol can be liberalized as far as just garment wear, because good results have been reported with a garment-only postoperative protocol [15].
- The final results are usually apparent by approximately 6 months postoperatively.

POTENTIAL COMPLICATIONS/RISKS/BENEFITS/LIMITS

- Limits
 - A wide range of fat graft volumes has been reported in the literature, from 240 mL to 900 mL per side [4,13,16], with reports as high as 1260 mL of fat graft per side [15].
- Benefits
 - Gluteal augmentation with fat graft can increase both projection and volume of the buttocks as well as change their shape. The aesthetic improvement is contingent on creation of a frame by liposculpture of the abdomen, waist, back, and thighs. Without the right frame, patients maintain their existing contour and only gain size.
 - Published series report an 80% to 90% satisfaction rate [13,17], high likelihood to recommend, and improvement in psychological well-being.
- Complications/management
 - Seroma
 - Seroma is the most common complication of this surgery, at a rate of slightly more than 3% [18,19], justifying the lower abdominal and presacral drains. If encountered, it is treated with aspiration and antibiotics if there is suspicion of infection.
 - Oil cysts/fat necrosis/graft resorption
 - Overinjection of fat graft either by not creating enough individual tunnels, thus letting it coalesce, or by exceeding the recipient site capacity [20] leads to poor take and degeneration of fat graft. There seems less risk of this in the gluteal recipient site because even larger parcels of graft appear to revascularize [15].
 - Infection
 - Overall rate of infection for this procedure is cited at less than 1% [19]. Only a minority of practitioners prescribe prophylactic antibiotics postoperatively [21]. No high-level evidence exists for this specific case, and the authors recommend treating it like any other routine clean body contouring surgery.
 - Contour deformity
 - Minor contour deformities may be treated with the equalization technique of using an exploded-tip cannula with no suction to redistribute the remaining fat [14]. If only recognized postoperatively, fat grafting of depressions or correction liposuction may be undertaken.
 - Pulmonary embolism/death
 - There is now more attention than ever paid to fatal fat embolism due to intramuscular graft placement. The frequency of this event was initially brought to light by a survey of Mexican surgeons showing 13 cases of fatal fat embolism among 378 respondents performing the procedure over a 10-year time span and 9 cases identified in Colombia by review of autopsy records over a 15-year span [22]. These findings and the rising popularity of gluteal auto-augmentation prompted the formation of an Aesthetic Surgery Education and Research Foundation task force to study the issue. The mortality rate of gluteal auto-augmentation due to fat emboli was estimated between 1:6241 and 1:2351 compared with the 1:55,000 overall mortality rate for all American Association for Accreditation of Ambulatory Surgery Facilities facilities [23].
 - Multivariate analysis of the survey responses indicated that the following variables were statistically significantly associated with fatal fat embolism: deep muscle injection (incidence rate ratio [IRR] = 4.03; $P < .0001$), angling the cannula downward (IRR = 3.90; $P < .0001$), and multiple-hole cannula (IRR = 2.46; $P < .0001$). Variables associated with decreased rate of fatal pulmonary embolism were mid to superficial muscle injection (IRR = 0.18; $P < .0001$), parallel angulation of the tip (IRR = 0.58; $P = .0255$), and cannula size greater than or equal to 4.1 mm (IRR = 0.20; $P = .0002$) [5].
 - In January 2018, a Multi-Society Gluteal Fat Grafting Task Force issued a statement providing recommendations to improve safety [24], including
 - Stay as far away from the gluteal veins and sciatic nerve as possible. Fat should only

be grafted into the superficial planes, with the subcutaneous space considered safest. If the aesthetic goal requires more fat than can be placed in the subcutaneous layer, the surgeon should consider staging the procedure rather than injecting deep.

- Concentrate on the position of the cannula tip throughout every stroke to assure there is no unintended deeper pass, particularly in the medial half of the buttock overlying the critical structures.
- Use access incisions that best allow a superficial trajectory for each part of the buttock; avoid deep angulation of the cannula; and palpate externally with the nondominant hand to assure the cannula tip remains superficial.
- Use instrumentation that offers control of the cannula; avoid bendable cannulas and mobile Luer-Lok connections. Vibrating injection cannulas may provide additional tactile feedback.
- Injection should only be done while the cannula is in motion to avoid high-pressure bolus injections.
- The risk of death should be discussed with every prospective Brazilian butt lift patient.
 - The practitioner is also advised to refer to selected publications for further background on the safety of this procedure [5,25,26].
- Gluteal augmentation techniques: autograft versus implant-based
 - Gluteal augmentation with the use of autologous fat grafting has a significantly lower rate of complications compared with implant-based augmentation (9.9%–10.5% vs 30.5%) [18,19].
- Fat graft donor site, harvest technique, and processing technique choices (Table 1)
- Fat graft placement
 - The dogma of fat grafting the face and breast has been small fat graft aliquots, meticulous tunneling technique, and avoiding overfilling [1,32]. Graft-to-recipient site ratios beyond 1:4 had a highly increased (9.5% or greater) fraction of fat parcels greater than 0.2 cm [20], which was believed at the upper limit of graft that will revascularize [32].
 - In gluteal lipofilling, use of as large as 5-mm cannula to place graft intramuscularly has shown long-term graft take with no significant oil cyst formation on magnetic resonance follow-up studies [15]. It is possible that larger grafts can survive in that environment or that minor fat necrosis may be better tolerated, with apparently good ability of any necrotic fat to be cleared by local tissues [4].
- Measures that can be taken to improve the safety of the procedure [5,33]
 - Patient selection
 - Patients who need dramatic improvements in gluteal projection and lack an appropriately sized recipient site may be better candidates for an implant-based augmentation. Providing the same results with autologous augmentation likely require excessive fat graft placement intramuscularly and, therefore, a higher risk of deep structure injury.
 - Cannula choice
 - A larger, blunt cannula is thought to be less likely to cause a vein laceration. Its increased

TABLE 1
Fat Graft Donor Site, Harvest Technique, and Processing Technique Choices: Current Evidence

Donor site choice	No evidence any specific donor site is superior [27,28]
Donor site infiltration with tumescence or lidocaine	Noninferior or possible slightly superior to dry technique [27–29]
Fat graft harvest using syringe vs suction-assisted liposuction (SAL) or ultrasound-assisted liposuction (UAL)	No evidence any method is superior [27–29]
Fat processing: washing vs centrifugation vs gauze rolling vs gravity separation	No evidence any method is superior [27–29]
Liposuction cannula size impact on fat graft viability	Larger size cannula may be superior [28,29]
Reinjection cannula size impact on fat graft viability	No difference any method is superior [27]
Cell-assisted lipotransfer	Overall level of evidence is low, with some studies suggesting improved graft survival [30,31]

stiffness translates to greater control by the surgeon, because thinner cannulae may bend and track deeper than intended.

- Lipofilling plane choice
 - Deep intramuscular fat graft injections are likely the technical component responsible for gluteal vein lacerations and fat emboli. Although it seems that injection in the superficial muscle layer is not associated with fat emboli [5], surgeons should be aware that it may be difficult, if not impossible, to tell the exact layer being grafted, so the decision to graft the muscle belly should be carefully weighed.
 - Avoid or minimize deep graft placement in the inferomedial quadrant of the buttock to minimized risk to the sciatic nerve and the inferior gluteal vessels [34].
- Lipofilling technique
 - The cannula must be kept parallel to the posterior surface of the thigh. Angling the tip toward the table to graft the muscle should be avoided at all times, because control of the depth is difficult and inadvertently deep passes may be made.

DISCUSSION

High-volume lipofilling is a body contouring modality that has come into its own with well-established applications for breast reconstruction or augmentation and for gluteal augmentation and shaping. The large (>1-L) grafts supported by the gluteal recipient site represent a dramatic advance in fat grafting. Evidence shows a markedly lower rate of complications with lipofilling compared with implant-based augmentation. The current science of fat grafting is composed overwhelmingly of data drawn from benchtop and animal models and from clinical results in the face and breast recipient sites. Research on lipofilling for gluteal augmentation is composed of level III and level IV studies and lacks high-quality trials to guide best practices [21].

Published series present several variations on the surgical technique presented in this article, such as tumescent solution composition, positioning sequence, and postoperative regimen [21]. Investigators also vary in their choice of aspiration cannula, aspiration method (syringe vs liposuction pump vs ultrasound-assisted liposuction), or fat graft processing methods, but, as summarized previously, there is

no strong evidence that these choices have an impact on graft survival. There is also wide agreement that most of the basic concepts of fat grafting technique hold true when transferring separate the words (large volumes), no hyphen volumes—these include use of low shear devices and careful graft placement in cross-hatched tunnels in multiple planes to avoid consolidation.

The technical points that can make a difference in the results and must be carefully considered by the surgeon include cannula size for graft placement, volume of graft transferred, and fat graft injection plane and technique. Even with a large subcutaneous adipose tissue recipient site, high-volume lipofilling usually requires placing graft into the muscle itself, which is the prevalent technique at this time [21]. The muscle recipient site allows for not only large volumes overall but also large tunnels and individual grafts, with cannula sizes as large as 5 mm routinely used [15,21]. This is in stark contrast to previous recommendations for thinner cannulae in the face and breast, where a smaller-diameter fat graft tunnel seems necessary for graft take [1,32]. These findings suggest the gluteus major recipient site does not abide by the limitations previously seen when lipofilling the adipose compartments of the face and breast [1,32,35].

The most important technical point at this juncture is intramuscular fat grafting. It is clearly the key to allowing high volume transfer and grafting the superficial muscle layer seems safe, but the consensus is that deep intramuscular injection is implicated in vein lacerations and devastating fat emboli [5]. It is unclear at this time how accurately a surgeon can tell the actual plane or injection, because some practitioners whose patients experienced fat emboli were convinced they had only grafted the subcutaneous plane [5]. Intramuscular grafting must be always balanced with the risk of inadvertent damage to the deep vessels and all the technique points discussed previously should be incorporated to maximize the safety of the procedure.

SUMMARY

High-volume lipofilling is an exciting technique and has found a popular application in gluteal augmentation. The excellent results demonstrated in the published series show that rapid lipofilling with larger cannulae into the subcutaneous and intramuscular recipient sites still produces graft take comparable with the traditional methods in the breast and face.

If choosing to graft the muscle, providers must take great care in their technique, avoid any deep passes, and incorporate the safety measures described in this article to minimize the risk of a potentially fatal fat embolism event. Further studies will hopefully provide evidence to guide technique refinement and improve safety.

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Filler Complications



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KEYWORDS

- Filler complications
- Filler ischemic complications
- Filler skin necrosis
- Filler blindness
- Hyaluronic acid gel filler
- Dermal filler complications
- Filler soft tissue ischemia

KEY POINTS

- Global filler safety includes understanding facial anatomy, patient selection, product selection, and product placement.
- Fillers function as implants; injectors should become familiar with the properties of individual fillers.
- Education, recognition, and treatment are important in addressing filler complications.
- Complications may occur after any filler injection, even in the hands of the most experienced injectors.
- Always have hyaluronidase available when injecting fillers.

INTRODUCTION

Dermal fillers represent a popular nonsurgical method for facial rejuvenation because patients and caregivers perceive them as simple and safe. In 2016, the estimated number of injectable filler procedures in the United States reached 2.7 million, according to the American Society for Aesthetic Plastic Surgery [1]. Hyaluronic acid gel fillers represented most, 2.5 million, of these injections. The supposed reversibility of hyaluronic acid gel fillers and the increasing variety of approved applications and formulations of these products add to their popularity. However, increasing use of these fillers will produce more of the less-common but significant complications observed with these filler products. Some of these complications can be devastating and irreversible, like scarring distant from the site of injection and blindness. Injectors should understand the complications associated with dermal fillers. Mild complications, such as contour irregularities and nodules,

occur relatively commonly; but severe complications, such as infections and ischemia, that may produce permanent cosmetic or visual deficits may also occur. Some complications may occur more frequently with certain filler products; therefore, the injector must understand the properties of each filler product injected. As the Food and Drug Administration has approved more than 25 dermal fillers [2], this represents an increasingly daunting task. Favorable properties, such as generally isovolumic, temporary, and reversible effects, have propelled hyaluronic acid gel fillers to dominate the filler product landscape. Each hyaluronic acid gel filler product possesses unique properties that produce a particular complication profile for each product [3]. Practicing global filler safety, including knowledge of the facial anatomy, patient selection, product selection, and product placement, can minimize complications.

Despite best practices, complications still occur. Thus, the informed consent process must include a

Disclosure Statement: The authors have nothing to disclose.

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detailed discussion of all the risks and potential complications. Further, early recognition and treatment of complications may limit their consequences. The injector, staff, and patients should understand the signs of complications, especially ischemic complications, and initiate prompt evaluation and treatment.

GLOBAL FILLER SAFETY

Although injecting facial fillers is an art, the accurate and safe placement of product depends on a thorough understanding of the patients' history as well as facial anatomy and the product's properties.

A thorough patient history will guide the decision to inject, the type of product injected, and the placement of the filler. A detailed filler history should be obtained, including the date, location and type of filler placed, as well as any adverse reactions to the filler. Some patients may not readily admit to recent fillers or may have forgotten this history, so it is important to explain the importance of this history to the patients. Previous facial surgeries should be noted, and any history of old trauma or scars should be documented as well. A history of facial, particularly eyelid, swelling should be elicited; patients should be specifically questioned regarding their recent use of anticoagulants and antiplatelet medications.

A detailed description of facial anatomy is beyond the scope of this article; however, it is imperative that the injector understands the underlying bony, soft tissue, and vascular anatomy when injecting fillers. Additionally, following recommended injection techniques, such as moving the tip of the needle or cannula at all times, having low injection pressure on the plunger, and injecting small amounts per pass, will allow for safer and more accurate product placement (Box 1).

COMPLICATIONS

Some investigators divide complications based on timing: early versus late [4]; however, dividing complications into nonischemic versus ischemic may represent a more clinically useful perspective [5] (Box 2).

NONISCHEMIC COMPLICATIONS

Nonischemic filler complications include nodules, granulomas, prolonged edema, the Tyndall effect (blue-grey hue), and infections.

BOX 1

Recommended Injection Techniques

1. Understand periorbital anatomy.
2. Inject small volumes per pass and less than 0.1 mL in any one area.
3. Keep moving the tip of the injection needle/cannula.
4. Attempt aspiration before injection, however, sometimes because of the length of the needle or nature of the filler product, may not produce a flashback
5. Use low injection pressure; do not force injection, especially in areas of previous scarring, injection, or surgery.
6. Consider the use of blunt cannulas, but remember they do not eliminate risk.
7. Smaller needles and cannulas may be more likely to penetrate vascular walls.
8. Always know where the tip of the needle or cannula is in 3 dimensions, including depth (can use nondominant hand to protect globe and feel the tip of cannula before injection).
9. Consider local anesthesia with epinephrine to vasoconstrict blood vessels; however, blanching may delay the recognition of ischemic complications.

NODULES/GRANULOMAS

Contour irregularities typically arise after unintended superficial product placement or inappropriate product selection (Fig. 1). Nodules often represent superficial collections of filler and appear as uninfamed, palpable, and often visible hemispherical lesions within 4 weeks of injection. Granulomas typically

BOX 2

Filler Complication Classification

Nonischemic complications

- Nodules
- Granulomas
- Prolonged edema
- Tyndall effect
- Infection
- Biofilm

Ischemic complications

- Skin ischemia/necrosis
- Blindness/visual compromise

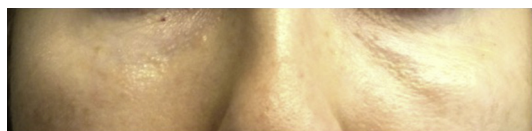


FIG. 1 Nodules. Nodules can be seen in the left periorbital area. The eyelid skin is the thinnest in the body and can show nodules/contour irregularities more readily.

develop later than this and typically present with inflammation and pain [4]. Hyaluronic acid gel fillers produce much fewer granulomas and hypersensitivity reactions than collagen and other fillers, so these complications occur much less commonly than in the past [4]. Massage may help flatten some nodules but if the nodule persists, removal of the filler product may be indicated. In cases of nonhyaluronic acid gel products, sometimes a needle nick over the nodule can express the causative material. In cases of hyaluronic acid gel filler, intralesional hyaluronidase injection can dissolve the filler product. Both human recombinant and animal-derived (bovine or ovine) hyaluronidases exist [6,7], and these products possess similar biological properties. The use of hyaluronidase to dissolve fillers is off label, but several reports substantiate its use for this purpose [8–11]. The amount of cross-linking of each hyaluronic acid gel filler product affects its reaction to hyaluronidase. The more cross-linked the product, the more resistance to degradation by hyaluronidase [12,13]. Dissolving a hyaluronic acid gel filler nodule typically requires only small amounts of hyaluronidase (10–50 IU) injection, which can be repeated if necessary [8,14]. In cases of granulomatous nodules, steroid and/or 5-fluorouracil injection may improve the lesions; however, each carries some risks, and this use is considered off label [15,16].

PROLONGED EDEMA

Transient edema as well as bruising is expected after filler injection. Prolonged edema, however, is not expected but may develop in patients with preexisting fluid deposits or propensity for fluid retention. Areas at higher risk for preexisting or posttreatment fluid retention include the lower eyelid and malar mounds/festoons (Fig. 2). Identifying patients at risk for prolonged edema after filler injections, by eliciting a history of such problems and with a detailed preinjection examination, represents an important step in the



FIG. 2 Prolonged edema.

evaluation of patients receiving the filler. If hyaluronic acid gel filler is used in such patients, the risks must be thoroughly discussed, and selecting a less hydrophilic product may decrease the risk of prolonged edema. If prolonged edema occurs, hyaluronidase can be used to dissolve the hyaluronic acid gel product; but it is not always successful.

TYNDALL EFFECT

The Tyndall effect, a misnomer, refers to a bluish hue within the injected area after hyaluronic acid filler injection in the periorbital region (Fig. 3). This effect typically occurs in thinner, lighter-skinned individuals. It can also occur after superficial injection in this region, though the effect may occur even after deeper injections, so patient counseling should include this risk. This bluish hue can also develop over time as the filler product migrates anteriorly. Additionally, individuals with greater degrees of skin pigmentation may occasionally develop a darker hue in the periorbital region after hyaluronic filler injection, which may represent a similar effect or perhaps represent a form of postinflammatory hyperpigmentation. Although in distressed patients

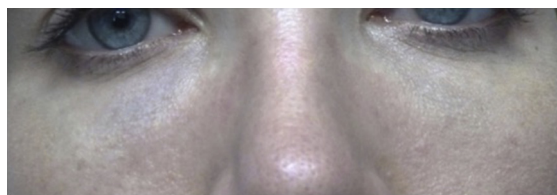


FIG. 3 Tyndall effect. Blue-grey hue apparent in the periorbital area bilaterally, secondary to hyaluronic acid gel filler.

hyaluronidase may improve the Tyndall effect, patient counseling should include the fact that any beneficial effects of the filler will also diminish and the periorbital hollows will return [17].

INFECTION/BIOFILM

Inflammation occurring at any time after filler injection should raise the suspicion for infection. Preparing the skin before injection to remove any makeup or dirt and using an antibacterial cleaning solution may minimize the risk of infection.

In cases of suspected infection, antibiotic treatment should begin immediately and consideration should be given to removing the filler, which may represent the nidus of infection. Although hyaluronidase can dissolve hyaluronic acid gel fillers, some experts recommend not injecting hyaluronidase in cases of active infection, as it could spread the infection [18]. Biofilms may also occur after filler injection and can manifest as smoldering inflammation and erythema (Fig. 4). If a biofilm is suspected, a tissue biopsy and culture may assist in the diagnosis; treatment may include removing or dissolving the filler and obtaining a consultation with an infectious disease specialist, as this type of infection may resist standard therapies [19].

ISCHEMIC COMPLICATIONS

Reports of various ischemic complications of fillers have existed for years; but with increasing use, less common but tragic cases of skin necrosis and blindness are being reported with increasing frequency. Although the incidence of vascular compromise remains unknown, this complication may occur in as many as 3 in 1000 injections [20]. The high-risk areas or danger zones include the glabellae, nasal area, nasolabial folds, and temple; but ischemia can occur anywhere on the face. Some recommended injection techniques may

minimize intra-arterial injection of filler, but no technique is 100% effective.

The mechanism of action of filler-induced ischemia is direct intra-arterial injection of the filler product [9,21].

Inadvertent needle penetration and injection within an artery produces both retrograde and anterograde flow. The retrograde injection of material may then move forward along a different arterial tributary that supplies a different region than the initial artery injected. Therefore, the ischemia occurs in a larger distribution than the focal area injected, as filler particles embolize forward in the vascular distribution of more than the one artery injected. This produces soft tissue ischemia and eventually necrosis of the skin or blindness if the ophthalmic artery is embolized. The danger zones for blindness include the glabellae, nose, nasolabial fold, and temple, as the arteries in these locations have a direct connection to the ophthalmic artery [20,22,23] (Fig. 5). The injector, but also the staff and patients, should understand the signs of ischemic complications to allow for prompt evaluation and treatment. Because this treatment includes hyaluronidase, the prepared injector must have hyaluronidase available at all times.

SOFT TISSUE ISCHEMIA

The signs of soft ischemia vary and may mimic other conditions, such as a bruise or herpetic infection, and include mottling, pain, blister formation, bluish discoloration, and, later, tissue blackening or necrosis. Whitening or blanching on injection as the filler product displaces red blood cells typically occurs only transiently and, thus, may escape observation by the injector. Pain does not always occur, as many patients receive topical or injected anesthetics and many filler products contain lidocaine. Usually, a fine reticular pattern in an area of vascular distribution occurs and



FIG. 4 Biofilm. Left cheek inflammation and erythema noted 4 weeks after filler injection.

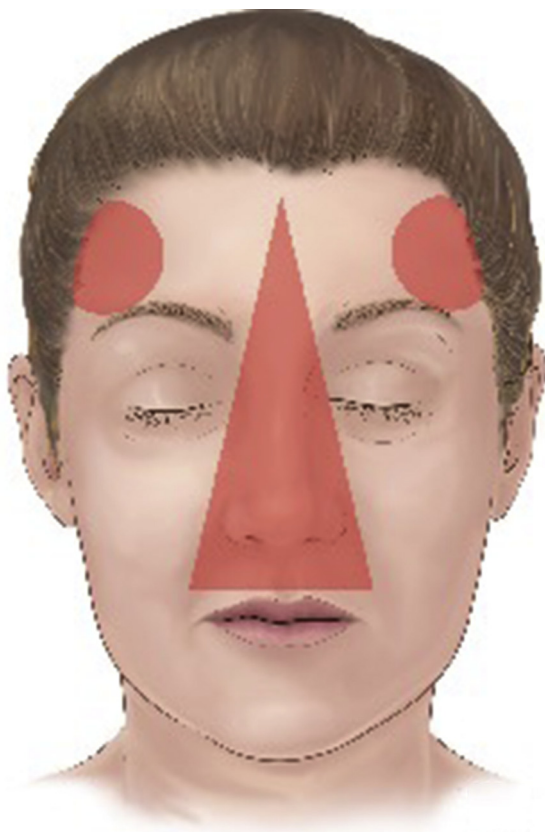


FIG. 5 Danger zones: blindness for filler injections. High-risk areas include glabellae, nose, nasolabial folds, and temples.

may be the first recognized sign of ischemia (Fig. 6A). This appearance typically sets in over several hours and may not occur until patients have left the office. The area appears darker as time passes and the ischemia progresses and may be confused for a bruise or a hematoma (Fig. 6B). In response to the ischemia, collateral vessels in the area dilate. Next, early skin necrosis results in superficial skin vesicles, which can be misinterpreted as a herpetic reaction. Recognizing if the skin changes follow a vascular distribution aids in the diagnosis of ischemia. Left untreated, the ischemia may lead to further skin necrosis and scarring, especially if the embolus involves the deep dermis. By the time an eschar forms, permanent scarring may result, even after treatment at this stage.

Injectors must prepare their staff and patients to understand the signs of soft tissue ischemia to allow for

prompt and effective treatment. Various treatment protocols have been suggested, including the use of aspirin, warm compresses, nitroglycerin paste and vasodilators, hyaluronidase, and hyperbaric oxygen [20,24]. Nitroglycerin paste and vasodilator treatment of filler-induced ischemia is controversial. Although nitroglycerin paste may successfully treat flap ischemia, the mechanism of this type of ischemia is different than that of filler-induced ischemia. Because filler-induced ischemia is the result of filler product within the vessels, dilation from nitroglycerin could cause further, more distal, embolization and consequent worsening of ischemia [25]. Further, nitroglycerin is mainly a veno-dilator and it can produce unwanted systemic side effects. Given the lack of good evidence for a benefit with nitroglycerin paste and the possibilities that it may worsen the condition or produce systemic side effects, such as hypotension, its use is not necessary.

The only proven treatment of soft tissue ischemia in cases of hyaluronic acid gel fillers is high-dose hyaluronidase injection, preferably within 24 hours of filler injection and at the latest 3 days afterward [26]. The authors advocates treatment of the entire ischemic area with 1500 IU hyaluronidase every 24 hours until the ischemia resolves. Others have suggested using 400 IU hyaluronidase every hour in the area of ischemia until capillary refill returns [10]. In patients presenting later than 24 hours and up to 5 days after filler injection, hyaluronidase may still reduce ischemia and scarring. In addition to regional infiltration of hyaluronidase, simultaneous intra-arterial hyaluronidase injection may result in more rapid ischemia resolution (Fig. 7). Intra-arterial hyaluronidase may find utility in the treatment of visual compromise, but its use for this complication is not proven. In patients treated with intra-arterial hyaluronidase injection, the authors discuss the risk of further embolization of the product if the filler product does not dissolve completely and choose patients carefully. Regardless of the method of hyaluronidase injection, treatment should be initiated early, given in high doses, and applied to the entire ischemic area. Hyaluronidase has also been used for treatment of ischemia from other filler types but may be less successful, as it does not dissolve those fillers.

BLINDNESS/VISUAL COMPROMISE

Filler-induced ischemia of the visual pathway represents a graver and more intractable complication

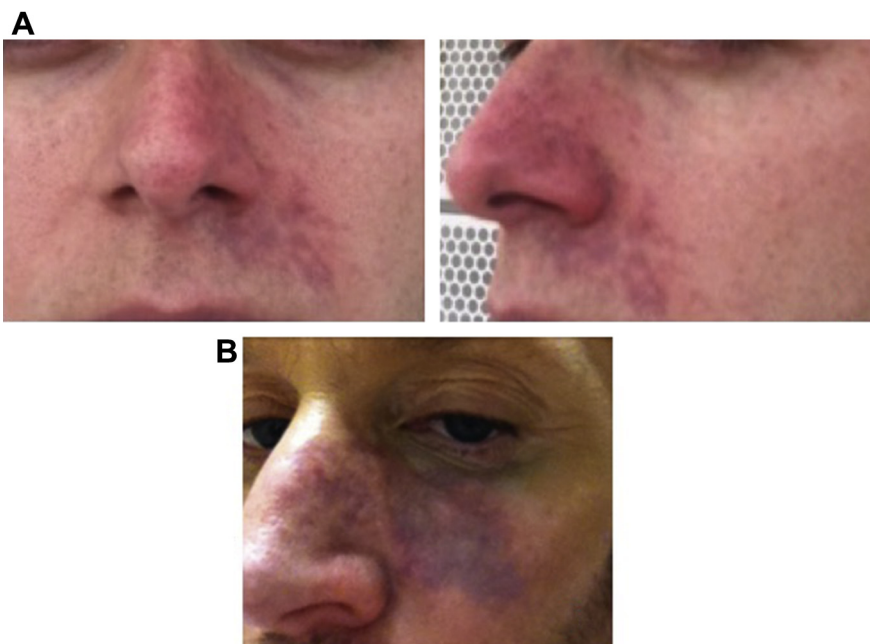


FIG. 6 Skin ischemia. **(A)** Early: pink reticular pattern following vascular distribution. **(B)** Later: purple ischemic area can be confused with a bruise.

than soft tissue ischemia. Unfortunately, reports of visual compromise have increased with the increasing use of filler products, and all injectors and prospective patients should be aware of this complication.

Patients with visual compromise present with immediate visual loss and can have other associated symptoms, such as headache, double vision (ophthalmalgia), droopy eyelids (ptosis), soft tissue ischemia, and stroke symptoms due to cerebral infarcts [22,27–33]. The most high-risk areas and danger zones for visual compromise are the glabellae, nasal area, nasolabial fold, and temple [22]. The mechanism of action is thought to be the same retrograde then antero-grade embolization of filler product discussed previously, but here occurring through the ophthalmic artery circulation. The level of obstruction determines the degree of effect and is likely related to the particle size of the filler.

Unfortunately, to date, no proven treatments exist to reverse blindness caused by fillers. As visual recovery from other embolic phenomenon is time sensitive, it is thought that retinal circulation requires restoration within 90 minutes to prevent permanent

vision loss. Methods used to treat embolic central retinal artery occlusion have been used to address filler-induced blindness. These measures include lowering intraocular pressure (IOP) with ocular massage, topical and systemic IOP lowering agents, as well as anterior chamber paracentesis [28]. In addition to standard treatments for retinal emboli, retrobulbar hyaluronidase has been used to treat blindness after hyaluronic acid filler injection but has thus far not proven effective, possibly because of the timing or lack of penetration of the material to the ophthalmic artery or intraocular circulation. Injecting hyaluronidase near or into the ophthalmic artery, via supratrochlear, supraorbital, or with interventional radiology, has also been proposed [34–36]. Other unproven treatments include corticosteroids, vasodilatory agents, anticoagulants, and thrombolytic agents [37]. Further investigation is needed to address filler-induced blindness.

Visual compromise or blindness mandates immediate referral to an ophthalmologist. Earlier recognition of this devastating complication may improve outcomes. Other ophthalmic signs, such as ptosis and ophthalmoplegia, often recover over time [38].

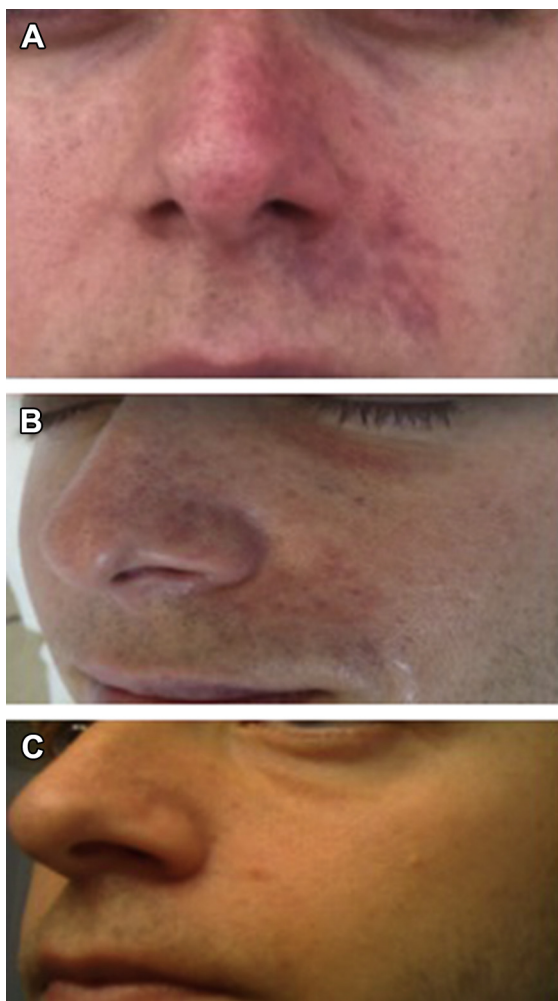


FIG. 7 Rapid resolution of hyaluronic acid gel filler ischemia with high-dose subcutaneous and intra-arterial hyaluronidase. (A) Initial presentation. (B) Twelve hours after hyaluronidase treatment. (C) Seventy-two hours after hyaluronidase treatment.

SUMMARY

Dermal fillers have achieved wide recognition and acceptance in facial rejuvenation. Increasing use will bring more complications. Understanding these complications, their mechanisms, and their treatments will allow for safer and more effective filler outcomes. Injectors should prepare their staff and their patients to appreciate the signs and symptoms of complications, especially ischemic complications, to allow for early and effective treatment. In addition, hyaluronidase should be available at all times when injecting fillers.

CURRENT CONTROVERSIES/FUTURE CONSIDERATIONS

The ideal filler possesses no complications, evolves with age to continue to address volume deficiency in a natural fashion, and allows for reversing if needed. The concept of global filler safety includes understanding the underlying anatomy, danger zones, and recommended injection techniques. These tools allow for safer and more effective treatment using these ubiquitous products. However, despite best practices, complications occur. Mitigating complications with early recognition and treatment can improve outcomes; however, at this time, blindness remains a devastating and largely untreatable complication of fillers. Further study may identify better treatments or products that can minimize this and other complications.

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Comprehensive Treatment of Scars and Other Abnormalities of Wound Healing

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KEYWORDS

- Burn and trauma scar
- Acne scar
- Surgical scar
- Atrophic scar
- Hypertrophic scar
- Laser therapy
- Scar rehabilitation
- Wound healing

KEY POINTS

- Scars are the inevitable result of healing after tissue injury and represent a significant medical problem around the world.
- The global burden of scarring is significant, leading to serious symptoms in patients, including disfigurement, psychological distress, pain, pruritus, and functional impairment.
- Scars can be due to acne or other inflammatory skin disease, surgery, and burn and trauma injuries. Scar mitigation must be addressed at every step along the journey with attention to every detail of healing to optimize the outcome with various therapeutic options depending on the type of scar.
- Multiple interventions can impact and improve the ultimate outcome of a scar. New innovative therapies have greatly improved the ability to help improve scars.



Video content accompanies this article at www.advancesincosmeticsurgery.com.

INTRODUCTION: THE IMPACT OF SCARS

Scars are the result of wounds that affect millions of people in the world and are prevalent in both civilians and wounded warriors. Scars can be cosmetically, psychologically, and physically incapacitating for the daily well-being of patients. The initial injury may be caused by trauma, surgery, burns, or a skin disease (acne, lupus, and so forth). After injury of the deeper dermis, a complex physiologic wound-healing cascade occurs, which causes scar formation. Once the healing cascade of inflammation, proliferation, and remodeling occurs, an immature scar is formed with significant type I

collagen. An immature scar tends to be erythematous often with mild pruritus and slightly elevated, relative to normal skin. In a few months, these scars may spontaneously improve to be flat and depigmented without any further symptoms [1]. The natural history of scar erythema and maturation after incisional and excisional wounds show surgical scars tend to fade within 7 months [2]. Surgical scars tend to improve over time; however, a hypertrophic scar may form as soon as 1 month after surgery, especially in areas of tension, such as the central chest or shoulder anatomic areas. The process of healing an acute wound through

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granulation tissue requires a delicate balance between degradation and deposition of extracellular proteins. Alterations in this process lead to abnormalities in scarring. Risk factors associated with scarring include specific anatomic location (chest, shoulders), infection, genetic susceptibility, and delayed healing. Hypertrophic scars and keloids (Figs. 1 and 2) are characterized by an increase in anabolic phase and accumulation of extracellular matrix. Burn and major trauma scars may grow up to 2 years after trauma, and these hypertrophic trauma scars form as early as 4 to 7 months after injury. Most keloids continue to grow for weeks to months and others grow for years.

Treatment of acute wounds includes systemic stabilization and surgery. Because of advanced medical and surgical care, patients with large body surface area involvement are now surviving. Because of a higher percentage of burn and trauma patient survival, large body surface areas and complex scars within functional deficits and symptoms now are seen that were never encountered before in medicine. Scars may exhibit symptoms, including pruritus, pain, decreased function, and limited range of motion (ROM). Innovative therapies are needed



FIG. 1 A 38-year-old African American man with an erythematous, hyperpigmented, hypertrophic burn and trauma scar located on his neck and face due to a gas explosion.



FIG. 2 A 21-year-old African American woman with a keloid scar due to ear piercings.

to treat this new generation of scar survivors. The main goal for scar treatment is that ultimate reconstruction can lead to recovery with optimum appearance and function. Numerous therapeutic options have been explored to improve all types of scars (Table 1).

Therapeutic approaches are being used for both the prevention and the treatment of scarring. Silicone gel sheeting, intralesional triamcinolone (10–40 mg/mL), cryotherapy, and pressure garments are all important treatment options for patients. Surgical techniques such as Z-plasty and W-plasty interrupt scar tension and remain mainstays for certain hypertrophic scars. Lasers have emerged to play an important role in scar rehabilitation. This article serves to provide a summary of the currently available options for prevention and treatment of scarring organized by type of scar.

CLINICAL APPROACH

Acne and Other Atrophic Scars

Acne vulgaris is a disease of the pilosebaceous glands. Scarring occurs when there is an innate immunity

TABLE 1
Treatment Modalities of Scars

Treatment	Mechanism of Action	Type of Scar Use Modality	Comments
Prophylaxis			
Silicone gel sheeting	Increased pressure, decrease fibroblast, and increased hydration	Prophylaxis for hypertrophic & keloid scars No effect on mature hypertrophic & keloid scar	Silicone gel is being studied vs silicone gel sheeting
Pressure therapy	Decrease collagen synthesis via apoptosis	Prophylaxis hypertrophic burn scars and keloids	Compliance challenge due to patient discomfort Continuous pressure (15–40 mm Hg) 23 h/d 6 mo to 1 y after injury
Therapies			
Corticosteroids	Anti-inflammatory effects & antimitotic effects fibroblasts & keratinocytes	Therapy for hypertrophic and keloid scars	May cause skin and subcutaneous fat atrophy
5-Fluorouracil	Increased fibroblast proliferation-apoptosis via inhibiting DNA synthesis	Therapy for hypertrophic and keloid scars	May cause liver toxicity, may not use in pregnant women
Bleomycin	Antimitotic effects on fibroblasts	Hypertrophic scars	Needs additional efficacy and safety studies
Scar revision	Surgery to change tension vector scar	Split or full-thickness skin grafting, Z-plasty, W-plasty, and linear excision	Excellent therapy for hypertrophic scars under tension and contracture scars Recurrence rates very high, if so, try excise keloid
Laser therapy	Multimodal laser therapy to target blood vessels and collagen	Therapeutic option for all types of scars	
Cryotherapy	Induction of tissue necrosis and decrease collagen synthesis	Spray or contact with liquid nitrogen 10–20-s freeze-thaw cycles	May cause permanent hypopigmentation in skin of color Novel approach is intralesional cryotherapy
Radiotherapy	Inhibition and apoptosis fibroblasts and inhibition vascular budding	Superficial radiographs, dosages of 15–20 Gy Electron beam Low- or high-dose brachytherapy	Best in early postoperative period May lead to increased risk of squamous cell skin carcinoma
Interferon	Inhibitor of collagen I and III synthesis: antiproliferative effects	Intralesional injections INF-alpha2b twice a day for 4 d	May cause flulike symptoms on injection: initial studies did not show statistical signs of improvement

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TABLE 1
(continued)

Treatment	Mechanism of Action	Type of Scar Use Modality	Comments
Mitomycin-C	Antiproliferative effects fibroblasts	Hypertrophic scars and keloids	May cause ulceration, needs more studies
Botulinum toxin A	Unknown mechanism of action: perhaps reduce skin tension and microtrauma	Prophylaxis surgical scars Mature keloids	Study showed 15 units BTA per 2 cm length of wound within 24 h had improved healing (Gassner and colleagues [14])

inflammatory response to the “trauma” caused by the acne formation. Inflammation is the single greatest reason for acne scar development. The greater the inflammation on the skin, the more likely scarring occurs because the skin is affected at a deeper level. Acneiform scars are the result of compromised collagen formation during the ordinary wound-healing process, resulting in cutaneous depressions. Topographic features of acne scarring include perpendicular bundles of collagen that anchor down the skin of the scars. There are various types of acne scars that include “ice-pick” scars, boxcar scars, rolling scars, and hypertrophic scars [3] (Table 2).

Acne scarring occurs as a result of damage to the skin during the healing of active acne. Risk factors for developing acne scars include genetic predisposition, delay in acne treatment, and behaviors by the patient with mechanical trauma (acne excoriée). Treatment of acne

scars must be customized for the patient depending on location and type of scars present. Atrophic scars are dermal depressions caused by loss of collagen due to inflammatory skin disease (cystic acne, varicella) [4]. Atrophic scars show thinning of the epidermis, collagen in dermis, and subcutaneous fat on histology [5]. Atrophic scars worsen with age because of natural lipoatrophy, which further emphasizes the scars. Many treatment options exist to improve acne scars (Table 3).

In 2001, Jacob and colleagues [6] reported that the best improvement in acne scars is noted when laser resurfacing is followed by one of the minor surgical interventions (punch excision, punch elevation, or subcision).

With the arrival of deep fractional resurfacing lasers, greater success of acne scars was achieved. Neo-collagenesis is stimulated the most from fractional laser therapy, thus making it the best choice for flat or thin

TABLE 2
Classification of Acne Scars

Scar Classification	Clinical Features	Comments
Atrophic		
“Ice pick”	Deep & narrow pitting (<2 mm) extend deep dermis or subcutaneous	60%–70% acne scars
Boxcar	Shallow (<0.5 mm) or deep (>0.5 mm) sharply demarcated vertical edges with wide base	20%–30% acne scars
Rolling	Superficial skin tethered by fibrous bands gives shadowing and sloped edges	15%–25% acne scars
Hypertrophic		
Hypertrophic	Pink to red, raised firm papules	Common on face if patient has excoriated and most common on chest, shoulders, and back
Spontaneous keloid	Red to purple, firm papules and nodules	Often central chest and shoulders

TABLE 3
Treatment Modalities for Atrophic Scars

Treatment	Mechanism of Action	Comment
Subcision	18-G 1.5-inch triangular cutting tip inserted and passed multiple directions to release fibrotic bands	Helpful for any depressed scar on the face, easy to perform
Punch excision or punch elevation	Scar excised with punch excision and closure to trade deeper scar for smaller linear closure	Mainly indicated for ice-pick and small boxcar scars
Nonablative laser therapy	PDL, nonablative fractional lasers reduce erythema and stimulate collagen	Ice-pick scars do not respond well to laser treatment
Ablative laser therapy	Produce deeper dermal effect and vaporization of scar with healing to almost normal skin	Superior to nonablative laser therapy
Chemical peels/CROSS treatment (chemical reconstruction of skin scars); usually CROSS is with 65%–100% trichloroacetic acid	Cause necrosis skin	Caution because often penetration not uniform Caution with darker skin types
Dermabrasion	Facial resurfacing abrades damaged skin for skin reepithelialization	Effective but operator dependent Risks are prolonged, with erythema, infection, and scarring
Injectable dermal fillers	Correct acne scars and skin texture by giving dermal fullness	Both temporary and permanent filler options available
Autologous fat transfer	Procurement of graft and placement of fat graft	Best for severely depressed scars
Topical retinoids	Vitamin A derivatives stimulate collagen formation	Recommended for all types of scars nightly
Needling	26-G to 30-G needle used to induce collagen formation	Best for rolling and shallow boxcar scars

scars. Acne scar techniques take a multiprocedural approach. Superficial strategies include glycolic acid chemical peels, topical tretinoin, and topical hydroquinone for skin surface improvement and pigmentary variation. Moderate approaches to address deeper scars include punch biopsies and closure (Fig. 3), Z-plasty, transposition flap, fat polysaccharide matrix or collagen, scar subcision, dermabrasion, Erbium, and CO₂ traditional laser resurfacing and fractional resurfacing. The goals of laser resurfacing are to stimulate collagen and help “plump” up these areas of collagen loss. Given the dermal pathologic condition presents with acne scarring, particularly with atrophic scars, treatment modalities should optimally be capable of affecting dermal remodeling at least 1 mm below the skin (Fig. 4). Patients with acne scars on their chest and back are often hypertrophic or keloidal (Fig. 5).

Ablative fractional CO₂ laser has been well studied for acne scarring. In a case series of 2 to 3 treatment sessions for moderate to severe acne scarring, clinical improvements of 26% to 50% have been observed in texture, atrophy, and overall improvements, and on topographic analysis. Improvements in scar depths of 43% to 79.9% were achieved with a mean depth improvement of 66.8%. A greater degree of improvement is seen with ablative fractional laser technology, as opposed to previous studies with nonablative fractional laser technology, which is thought to result from the deeper dermal penetration of the fractionated ablative CO₂ devices. Ortiz and colleagues particularly noted that patients treated for deeper scars on the cheeks with higher energy levels on the second and third treatments received the highest improvement scores [7]. Side effects with the ablative fractional device

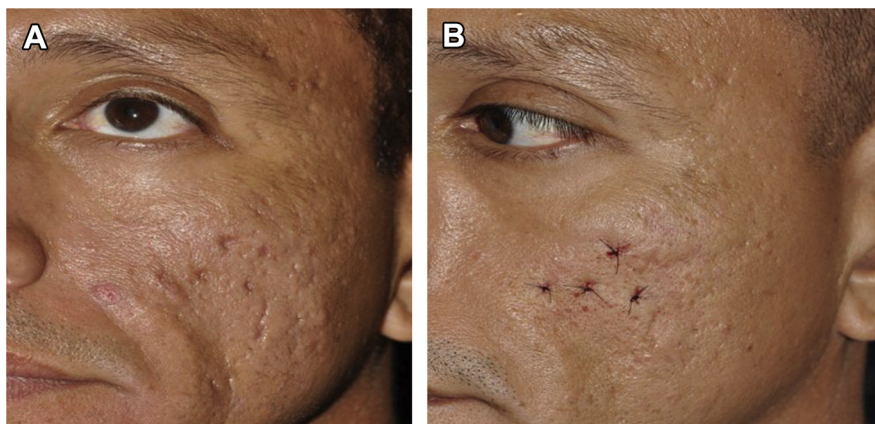


FIG. 3 (A) A 43-year-old Hispanic man with boxcar acne scars located on his bilateral cheeks. (B) Same patient immediately after 3-mm cutaneous punch biopsies for boxcar acne scars located on bilateral cheeks. Sutures usually remain on the face for 5 to 7 days. Often laser resurfacing can be done the same day as suture removal.

were mild to moderate, including posttreatment erythema, edema, and petechiae, all of which resolved within 7 days after each treatment. Correlating with this clinical data, in vivo studies by Hantash and colleagues [8] with this device have shown tissue ablation and thermal effects as deep as 1 mm into this skin, likely accounting for the effect on moderate to severe acne scarring observed.

Surgical scars

Most surgical scars will improve spontaneously over time. Only a small number of surgical scars will hypertrophy or atrophy. Hypertrophy may occur as soon as 1 month after a surgical procedure. The optimal timing for intervention has yet to be determined. Many patients use silicone gel or sheeting for prophylaxis. Nouri and colleagues [9] found in a split-scar study at the time



FIG. 4 (A) A 66-year-old Caucasian woman with a combination of atrophic acne scars, boxcar acne scars, along with texture irregularities on full face. (B) Same patient after 2 laser treatments with an Er:YAG laser (Joule Traditional, Action, Inc, Palo Alto, CA, USA) with laser-assisted drug delivery of poly-L-lactic acid immediately after laser treatment of the atrophic scars.

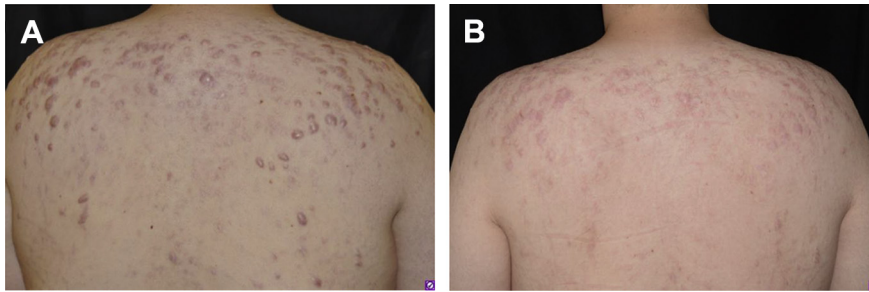


FIG. 5 (A) A 23-year-old Caucasian man with a combination of atrophic, boxcar, and hypertrophic acne scars on back. (B) Same patient after 2 laser treatments of nonablative PDL (Vbeam Perfecta, Candela/Syneron, Wayland, MA, USA) in combination with fractional ablative CO₂ laser (Lumenis UltraPulse, Yokneam, Israel; Deep FX and Active FX) with laser-assisted drug delivery of triamcinolone acetonide 10 mg/mL immediately after laser treatment of the hypertrophic scars.

of surgery that the pulsed dye laser (PDL)-treated side of scar healed better than the untreated control side.

In the surgical scar, evaluation of the elevation (hypertrophic) or depression (atrophic) of the scar is critical. The thicker hypertrophic scars need deeper treatment depths, whereas atrophic scars can be treated more superficially. Both hypertrophic and atrophic scars will benefit from multimodal laser treatment. Another characteristic that needs to be determined is the color of the scar. Early surgical scars with significant erythema respond primarily to vascular lasers with or without same day treatment of fractional lasers (Fig. 6). Early surgical scars with significant hyperpigmentation in them respond well to nonablative fractional lasers (Fig. 7).

Jung and colleagues [10] conducted a study of 23 Korean women with thyroidectomy scars; each was treated in a single session of 2 passes with a fractional CO₂ laser with a pulse energy of 50 mJ, and density of 100 spots/cm². All treatments were performed 2 to 3 weeks after surgery. Three months after fractional

CO₂ treatment, 12 out of the 23 study subjects showed significant clinical improvement greater than 51%.

Laser treatments are repeated at 1- to 2-month intervals with repeat evaluations of the scar's response to therapy at each visit. Normally after a series of 2 to 4 treatment sessions, the scar is significantly improved, and the physician can plan future treatments as needed.

Burn and traumatic scars

When treating burn and trauma patients, it is crucial to be mindful of what their challenges are after their wounds are closed, which then determines their quality of life. Burn scars can create significant morbidity and remain as a permanent reminder of the injury that has occurred. Diligent, professional wound care in the acute setting followed by time and assiduous scar management with conventional modalities, such as physical therapy, intralesional steroids, and surgical revision, can alleviate some of the effects of these scars. However, despite the standard of art care these patients have received, burn and trauma patients often suffer from severe pruritus,

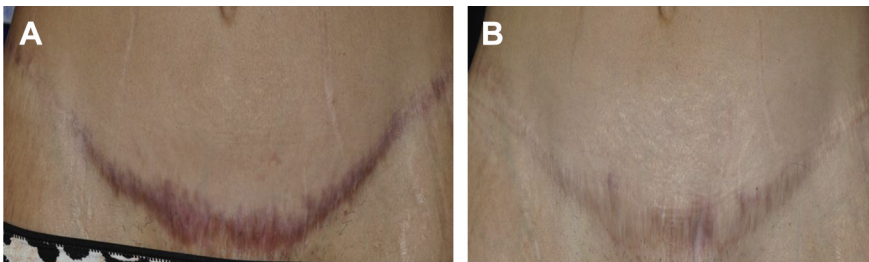


FIG. 6 (A) A 53-year-old Hispanic woman with a combination of erythematous, hyperpigmented, hypertrophic surgical scar from abdominoplasty. (B) Same patient after 3 laser treatments of nonablative PDL (Vbeam Perfecta, Candela/Syneron) in combination with nonablative fractional laser (Thulium 1927 nm; Solta Medical, Hayward, CA, USA) and fractional ablative CO₂ laser (Lumenis UltraPulse; Deep FX and Active FX) for the surgical scars.

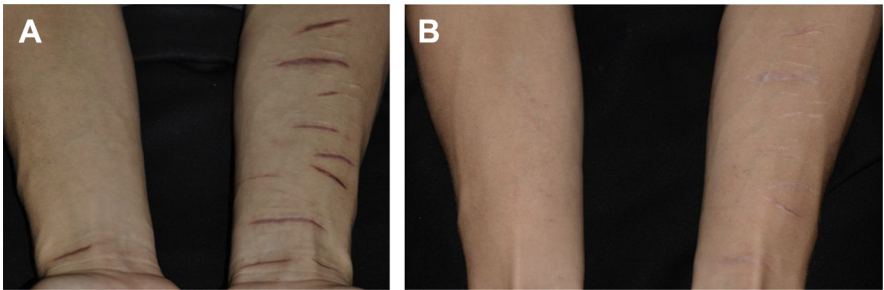


FIG. 7 (A) A 20-year-old Caucasian man with erythematous, hyperpigmented self-inflicting surgical scars on bilateral anterior forearms. (B) Same patient after 4 laser treatments of nonablative PDL (Vbeam Perfecta, Candela/Syneron, Wayland, MA, USA) in combination with nonablative fractional laser (Fraxel 1550 nm; Solta Medical, Pleasanton, CA, USA).

neuropathic pain, and contractures with restrictive ROM from their scars. All of these factors may have detrimental physical, aesthetic, and social impacts on their daily life. Advances in medical care have led to unprecedented survival rates after a wide range of injuries, such as burns, and battlefield injuries, further widening the gap in the treatment of severely scarred patients.

Burn and trauma wounds that take 21 days or more to heal have a 70% chance (or greater) risk of developing into a hypertrophic scar [11]. Keloids may arise from very small injuries or even mild skin irritations,

such as insect bites or skin infections. Physicians should always be cautious when taking care of a patient with a personal history of keloid scarring. Stretching of a wound also evokes inflammation in the dermis, which increases the risk of scarring. Wounds may be stabilized with compression garments, silicone gel sheeting, or neurotoxin. Once a hypertrophic or keloid scar has formed, surgery, corticosteroid or 5-fluorouracil injections, and laser therapy, and/or combinations of these modalities may be required for optimal results (Table 4).

TABLE 4 Treatment of Hypertrophic and Keloid Scars		
Treatment		
Surgery	Good releasing linear scar contractures and tension	Possible recurrence or worsening of scar (keloid)
Corticosteroid injections	Atrophy of collagen	Rapidly reduce scar volume Can cause atrophy, hypopigmentation, and telangiectasia
5-Fluorouracil injections	Apoptosis of collagen	Contraindications include anemia, leukopenia, thrombocytopenia, pregnancy, bone marrow suppression, and infection
Laser therapy	Millisecond-domain PDLs and similar devices that produce selective photothermolysis Ablative or nonablative fractional lasers that produce arrays of nonselective, microscopic thermal damage zones throughout the epidermis and dermis	Laser-stimulated tissue remodeling shares features with wound repair and with skin morphogenesis
Radiation therapy	High-dose-rate brachytherapy and electron beam radiation	Mainly keloid therapy, adjunctive Important, prevents secondary carcinogenesis
Compression therapy	Limit skin stretching during healing, reduce tension, and keep scar moist	Surgical tape, bandages, garments, silicone gel sheeting
Camouflage therapy	Makeup therapy	Inexpensive

When contraction is significant, and hypertrophy is present, surgical relief of tension is usually an essential early step in scar rehabilitation. After successful tension relief has been accomplished, hypertrophic scars mature more favorably and become more elastic. The relief of tension results in the immediate and ongoing remodeling of collagen. Improving scar quality with tension relief by either Z-plasties, or release and grafting, decreases the need for scar excision. Surgery is very good at improving severe scars, relieving severe contractures, and improving contour abnormalities (Fig. 8). Following tension relief and the subsequent improvement of scar maturation, the stage is set for further scar rehabilitation using laser therapies of different types for specific indications. Lasers have many advantages over surgery in this phase of scar rehabilitation. Laser treatment can be performed as an outpatient procedure without interrupting work or school. Multiple treatments provide gradual and steady improvement. The endpoint of treatment is at a potentially higher level because lasers allow for progressive benefit without the negatives and possible complications of surgery (Fig. 9, Video 1).

All scars have similar characteristics that make them amenable to improvement by the use of laser therapies.



FIG. 8 A 38-year-old Caucasian woman immediately after Z-plasty surgery for hypertrophic scar located on her right chest.

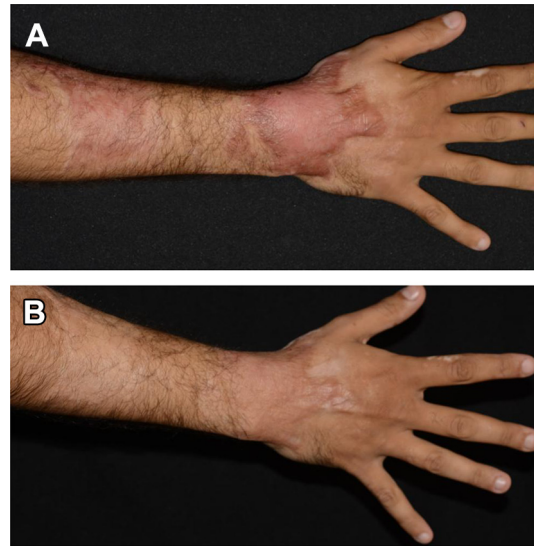


FIG. 9 (A) A 27-year-old Hispanic man with a burn and traumatic scar located on his right forearm and hand due to a cooking oil explosion. (B) Same patient after a series of 4 laser treatments of nonablative PDL (Vbeam Perfecta, Candela/Syneron, Candela, Wayland, MA, USA) in combination with nonablative fractional laser (Thulium 1927 nm; Solta Medical, Pleasanton, CA, USA), and Er:YAG laser (Joule ProFractional Inc, Palo Alto, CA, USA) with laser-assisted drug delivery of triamcinolone acetonide 10 mg/mL to help decrease the hypertrophy of the scar in conjunction with the laser.

All scars have pigmentary abnormalities, surface irregularities, abnormal vasculature, increased type 1 collagen, and usually some degree of contraction, often associated with contractures. Lasers can be used precisely and effectively to treat, and favorably modify, all of these abnormal scar characteristics. The essential problem is to clearly understand which laser should be used, how to use it, and when to use it, in order to obtain the maximum benefit for the patient with the least possible morbidity.

Laser treatments can improve both the function and the appearance of scar deformities, enabling patients to return more closely to their premorbid state, the true goal of reconstructive therapy. Diffuse contractures, abnormal pigmentation, persistent erythema, conspicuous meshed skin graft surfaces, and scar atrophy all seem to respond positively to appropriate laser treatments (Fig. 10).

SURGICAL TECHNIQUE: MULTIMODAL SCAR MANAGEMENT

Preoperative Planning/Considerations

Before any treatment, there needs to be an informed consent reviewed and signed that discusses the patient's

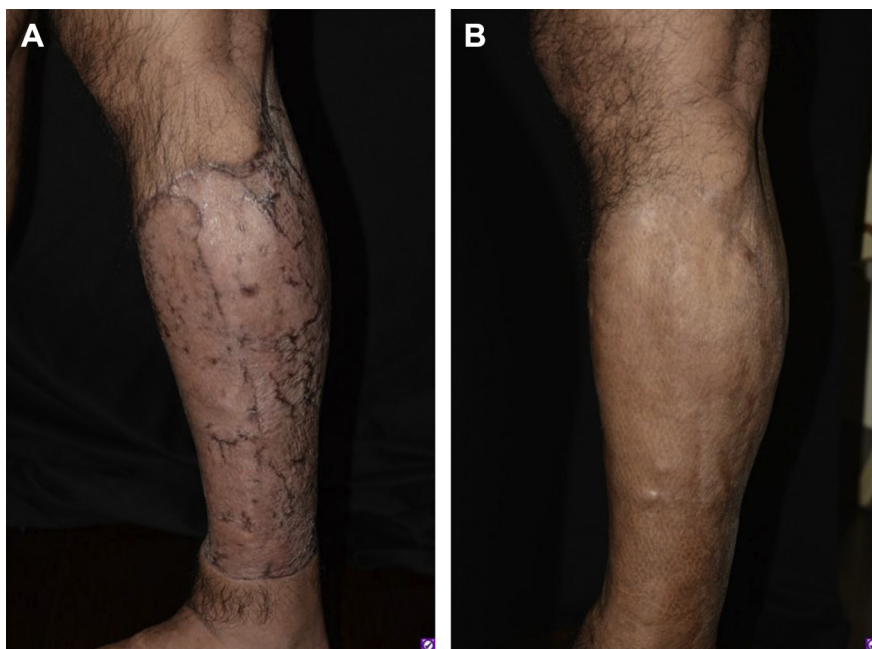


FIG. 10 (A) A 31-year-old Hispanic man with a burn and traumatic scar located on his left lower leg due to gas tank explosion in his truck. (B) Same patient after a series of 10 laser treatments of nonablative PDL (Vbeam Perfecta, Candela/Syneron, Candela, Wayland, MA, USA) in combination with nonablative fractional laser (Thulium 1927 nm; Solta Medical, Pleasanton, CA, USA), and fractional ablative CO₂ laser (Lumenis UltraPulse; SCAAR FX and Active FX, San Jose, CA, USA) with laser-assisted drug delivery of triamcinolone acetonide 10 mg/mL immediately after treatment to help decrease the hypertrophy of the scar in conjunction with the laser.

optimal goals, limitations, and potential complications. A team approach is vital for the patient, which may include many health care professionals, especially wound care specialists, physical and occupational therapists, compression garment experts, psychologists, psychiatrists, internal medicine and surgical consultation, being available if required throughout the course of treatment to optimize outcomes.

Relevant historical and physical information during the initial consultation is crucial to obtain; this includes the time and mechanism in detail of injury, surgical history, upcoming procedures, previous complications, current limitations, treatment goals, pain and sensory issues, presence of posttraumatic stress, and response to current therapy. Physical examination should elicit scar characteristics, such as the presence of residual erosions and ulcers, erythema, pliability, textural irregularity, hyperpigmentation, hypopigmentation and scar thickness, and degree of restriction. Having a physical therapist document ROM at baseline and as treatment progresses is very helpful in assessing scar improvements. Functional relationships, such as proximity to orifices and free edges, association with prosthetic

devices, and ROM limitations across joints, are also important.

As with any cutaneous surgical procedure, basic contact and hygiene safety measures should be emphasized to the patient. Oral antibiotics, antivirals, and antifungals are considered for use for prophylaxis starting 1 day before treatment and continuing up to 1 week on a case-by-case basis. Current principles of antibiotic stewardship would recommend against the use of oral antibiotics prophylactically and that they be reserved for infectious complications. In the authors' experience, it is possible to develop scar complications, and the authors have seen scarring from other physicians who failed to recognize and treat infections, which is why each physician must make decisions on a case-by-case basis. When treating facial areas, viral prophylaxis should be considered, especially if the patient has a personal history of herpes simplex I (HSV I). In addition, prophylaxis may be given if the patient is traveling a long distance to receive treatment, has history of infections (methicillin-resistant *Staphylococcus aureus* or HSV 1), or is treated on large body surface areas.

It is recommended to have the patient have the following items for treatment day:

1. Photo-protection should be advocated for, including avoidance in the early posttreatment period, and application of gentle sun blocks once epithelial integrity is restored (approximately 2–3 weeks' after laser treatment). Physical sun blocks that contain zinc or titanium dioxide are less irritating to newly lasered skin and are vital to a patient's aftercare. Scars in skin of color are very susceptible to hyperpigmentation.
2. Compression therapy while healing from laser with silicone gel sheets, tight athletic wear, or tailored medical compression garments are also recommended for patients.

Preparation and Patient Positioning

Most scar treatments are performed in an outpatient clinic setting. Once the procedure planning and considerations are completed before the treatment appointment, the preparation for treatment begins in office. Once the patient arrives, photography of the treated area is mandatory before treatment. With these photographs, the physician must evaluate the following:

- Dyschromia (erythematous, hyperpigmented, or hypopigmented)
- Type of scars (hypertrophic, keloid, flat, or atrophic)
- The body location of the scar (face, neck, leg, and so forth)
- Patient characteristics (skin type, comorbid conditions)

Next appropriate anesthesia (topical anesthetic preparations, injectable local anesthesia, and oral analgesia) should be discussed and given to the patient based on the treatment of scar, patient's age, and body surface area involved. Scar treatments, techniques, and adjunctive treatments should be applied thoughtfully to each patient. Each treatment is customized at every session according to individual scar characteristics and interval changes (Video 2).

REHABILITATION AND RECOVERY

Multimodal Scar Approach with Algorithms

Lasers have emerged as an important tool to improve scars. Pathologic scarring currently involves standard prophylactic and therapeutic strategies comprising compression therapy, silicone, intralesional injections of antimetabolites, cryotherapy, radiation, lasers, and surgical excisions. Most scars will require various combinations of these methods [12].

The optimal time to begin fractional laser treatment has yet to be determined. As a general rule, there should be a healed and intact epidermis before laser treatment. Younger, less mature scars are less tolerant of aggressive treatment and should be treated more judiciously. Mature scars, whether 1 year old or 60 years old, respond well to laser therapy.

POTENTIAL COMPLICATIONS/RISKS/LIMITS/BENEFITS

One of the benefits of laser therapy is the very low adverse event rate with vascular and fractional laser procedures [13]. Routine side effects after fractional laser therapy include the abrupt onset of transient erythema and localized swelling. It is important to let the patient be aware that even though swelling may resolve within 1 to 2 weeks, prolonged erythema may last up to 3 months after the procedure. Pinpoint bleeding after ablative fractional laser (AFL) can occur, but it is more ephemeral with the fractionated CO₂ laser due to the increased zone of coagulation compared with Er:YAG. A mild serous discharge is relatively common for 1 to 2 days after AFL treatment, so nonstick dressings with judicious taping may be considered depending on the location. Keeping the treated area moist can help prevent crusting and subsequent scarring. Pain after the procedure is usually minimal, although some patients describe mild intermittent itch for up to several days after the procedure. If pain after the procedure extends longer than a few hours, it is recommended for the patient to contact the physician. Infrequent side effects include prolonged erythema, pain after the procedure requiring medications, scar exfoliation, and transient postinflammatory hyperpigmentation.

SUMMARY AND FUTURE DIRECTIONS

Scar rehabilitation is aimed at the improvement of scars, and both physicians and patients must realize that some degree of scarring will remain after treatment. Scar rehabilitation by surgery and laser is a process that occurs over time and with multidisciplinary collaboration. With the combination of time, patience, and cooperation, the success of scar improvement will come. The skin is a dynamic organ; however, when it is injured, it has a limited ability for regeneration and the resulting scarring leads to aesthetic and functional issues. Cutaneous scarring may be atrophic, hypertrophic, or keloidal. The severity of scar that develops is influenced by a host of factors, including individual genetic predisposition, severity and type of injury, interventions, and

complications during the healing process. Every treatment given from the point of injury will influence the healing of a scar. Scar management is an ongoing process, which takes time for the skin to recover and function. The clinical decisions to choose which intervention to help scars involve planning with the patient. The timing of surgery is complex because it may involve downtime in a patient's life. Pressure garments, injections, topical silicone gel, massage, and laser therapy may all be done on an outpatient basis. The implementation of innovative therapies, including novel cell-based therapies, is continually improving to help scar patients. Continued research and innovations will allow the scar management teams to select treatment algorithms that will give their scar patients optimal outcomes and the hope to return to their lives.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.yacs.2018.02.017>.

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Advances in the Treatment of Melasma

An Evidence-Based Approach

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KEYWORDS

• Melasma • Laser • Light • Hyperpigmentation • Pigmentary disorders

KEY POINTS

- Melasma is a chronic and dynamic condition involving hyperactivity of melanocytes and deposition of melanin within the epidermis, dermis, or both. Clinically, it presents as focal hyperpigmented patches most commonly on the face. Well-established risk factors include sun exposure, oral contraceptives, pregnancy, family history, and Fitzpatrick skin types (III–V).
- The goal for effective treatment of melasma includes removal of the excess melanin in the epidermis and dermis as well as suppression of further melanogenesis. Without these 2 steps, there is high risk for relapse of melasma after treatment.
- Topical therapy remains the gold standard for first-line therapy for melasma using broad-spectrum sunscreens and either hydroquinone 4% cream, tretinoin, or triple-combination creams.
- In recalcitrant cases and in dermal melasma, the addition of laser treatment using low-fluence QS-Nd:YAG laser or other pigmented specific laser and light devices can be used.
- Melasma is difficult to treat and single-modality treatment approaches usually do not yield favorable long-term results.

INTRODUCTION

Melasma, formerly known as chloasma, is an acquired hyperpigmentation disorder most commonly affecting women. It is characterized by irregular brown to brown-gray macules and patches on the face, in 3 predominant clinical patterns: centrofacial, malar, and mandibular [1]. Of these patterns, the centrofacial is most common and involves the forehead, nose, upper lip excluding the philtrum, cheeks, and chin [2,3]. The malar pattern involves the malar cheeks, and the

mandibular pattern involves the jawline and chin. More recently the term “extrafacial melasma” has been used to describe a melasma pattern occurring on nonfacial body parts [4].

Although the exact cause of melasma is unknown, risk factors are well established and include sun exposure, Fitzpatrick skin types III to V, family history of melasma, pregnancy, and exogenous hormones (oral contraceptives and hormone replacement therapy) [1–3,5,6]. Recently, reports of visible light inducing

The authors have no relevant financial disclosures.

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increased and sustained pigmentation in the skin highlight another potential risk factor for melasma development and persistence [7,8].

Melasma, has been classified into epidermal, dermal, and mixed-type based on the location of pigment deposition [1]. In the epidermal form characterized by brown color, melanin is found in the basal and suprabasal layer. In dermal melasma, clinically more blue-gray in appearance, melanin is found in the superficial and deep perivascular melanosomes. Mixed-type melasma is characterized by both epidermal and dermal pigment deposition. Woods lamp (340–400 nm) examination was thought to enhance epidermal melasma lesions and aid in distinguishing it from dermal melasma, in which the pigment does not enhance with Woods lamp. However, recent study suggests that Woods lamp examination does not accurately detect dermal melasma as well as previously thought [9]. The location of excess melanin is important clinically, as it can guide treatment choice. The epidermal form is easier to treat and more amenable to topical therapy, whereas the dermal or mixed type of melasma is more resistant to treatment. It is thought that it is the presence of the deeper, dermal melanin that contributes to the difficulty in melasma treatment [1]. This is because destruction of these melanosomes is often accompanied by significant inflammation that in turn stimulates further melanogenesis [10].

Aside from the clear role that melanocytes and melanosomes play in pathogenesis of melasma, there is increasing evidence that melasma also has a significant vascular component. This has been demonstrated by the increased number and size of dermal blood vessels in melasma lesions compared with unaffected perilesional skin, as well as greater expression of vascular endothelial growth factor in keratinocytes of melasma lesions [11]. Furthermore, the study by Kim and colleagues [11] found a significant relationship between the number of blood vessels and pigmentation in melasma. The exact mechanism and relationship between this vascular phenomenon and melasma is not yet fully understood and is the subject of ongoing investigation.

Various treatments, including topical, oral, resurfacing techniques, as well as numerous light and laser treatments have been used for treatment of melasma, both alone and in combination. Unfortunately, treatments have often produced inconsistent and generally unsatisfactory results, and to this day achieving long-term clearance in melasma remains a clinical challenge. Given the clinical and therapeutic challenges of patients

with melasma, we present a practical approach to the evaluation and treatment of these patients, focusing on the most effective, safe, evidence-based treatments available currently for melasma.

PRETREATMENT PLANNING

Patient History

Given the complexity of melasma and interplay of both genetic and environmental factors in pathogenesis of the disease, a thorough history and physical examination of the patient is of utmost importance. History should include investigation of onset or worsening of hyperpigmentation and any relationship to pregnancy or the initiation of hormone therapy of any type. It is recommended that patients who develop melasma while taking an oral contraceptive pill stop the medication and avoid future use of similar drugs if possible [6]. Patients also should be asked about presence of previous inflammation at the hyperpigmented sites, as this can point away from diagnosis of melasma. Furthermore, extent of ultraviolet light exposure and patient's compliance with daily sun protection should be assessed. Importance of strict photoprotection before, during, and after the treatment must be reviewed and emphasized to all patients. Patients should understand that failure of appropriate compliance with strict photoprotection can lead to recurrence and at times worsening of hyperpigmentation after treatment. Patients' medications also should be carefully reviewed for presence of any phototoxic medications, as drug-induced pigmentation can be confused for melasma. Given that family history is an important risk factor for development of melasma [12,13], patients should be asked about family members who have had similar symptoms, which can help support the diagnosis of melasma.

Physical Examination

Pretreatment physical examination should include assessment of patient's Fitzpatrick skin type, because patients of darker skin types with melasma (Fitzpatrick type IV–VI) are at a higher risk of adverse events after treatment [14,15], including postinflammatory hyperpigmentation (PIH) and melasma recurrence, and extreme caution should be exercised in selecting the appropriate treatment modality in these patients. Because assessment of melasma involvement can be more challenging in skin of color, Woods lamp examination can be helpful in better visualization of hyperpigmentation (in all Fitzpatrick skin types.)

Furthermore, skin should be examined for presence of other concomitant inflammatory disorders, which can coexist in patients with melasma and influence the selection of appropriate therapy. Conditions clinically mistaken for melasma include PIH, photo-induced drug eruptions, actinic lichen planus, lichen planus pigmentosus, pigmented contact dermatitis (Riehl melanosis), exogenous ochronosis, erythema dyschromicum perstans, or acquired bilateral nevus of Ota-like macules (Hori nevus). In cases of diagnostic dilemma, a skin biopsy may be helpful in establishing the diagnosis and appropriate referral to a dermatologist should be considered.

Treatment Approach

Successful and long-term treatment of melasma is difficult. Previously reported treatment modalities, including topical, oral, resurfacing techniques, light and laser treatments, have produced inconsistent or short-lasting results. Furthermore, given potential for accompanying skin irritation, some treatments can lead to further worsening of cutaneous dyspigmentation or even scarring. A systemic Cochrane review [16] concluded that the quality of studies evaluating melasma treatment was generally poor and that the large number of different treatments evaluated showed that there is no standard therapy for melasma. Given lack of sufficient, randomized, placebo-controlled trials and long-term studies to yet define a clear and standardized guideline for treatment, the following is a current evidence-based approach to melasma treatment.

TOPICAL THERAPY

Topical therapy, including photoprotective products, are generally first-line treatments for melasma. In general, topical therapy is thought to be most effective for epidermal type of melasma.

Sun Protection

Treatment of melasma usually begins with sun avoidance and meticulous photoprotective measures against both UV and visible light. Application of a broad-spectrum sunscreen (SPF 50+, UVA-PF 28) on its own has been shown to not only decrease the incidence of melasma during pregnancy but also result in improvement of preexisting melasma in pregnant patients [17]. Furthermore, recent studies have shown that visible light can result in hyperpigmentation lasting as long as 3 months, thus photoprotection in patients with melasma should include ingredients that protect

against visible light (such as iron oxide) in addition to traditional ingredients that protect against UV light [7,18,19].

Depigmenting Agents

Hydroquinone

The most extensively studied depigmenting agent, hydroquinone works by blocking the enzyme tyrosinase, the key enzyme in melanogenesis. Hydroquinone is available as a prescription 4% formulation, as well as an over-the-counter 2% formulation, and is usually dosed twice daily. In a randomized, double-blind placebo-controlled trial, the use of hydroquinone 4% for 12 weeks was shown to result in complete clinical response in 38% of patients with melasma compared with 8% of those who used placebo [20]. In another randomized, double-blind, placebo-controlled trial, Vazquez and Sanchez [21] demonstrated that the addition of daily sunscreen augmented hydroquinone's efficacy in improving melasma in 96% of participants versus 80.7% of those who used hydroquinone alone. Practitioners should be aware of the potential of hydroquinone to cause skin irritation, as well the debate regarding its safety with chronic use. Despite the history of controversy and concerns for safety both in Europe and the United States surrounding the potential of hydroquinone to cause exogenous ochronosis (EO) in humans, and its possible carcinogenic potential in genetically susceptible rat models, human studies as well as the National Toxicology Program have failed to show evidence of carcinogenicity in humans exposed to hydroquinone [22]. Furthermore, evidence from documented cases of EO from the start of its use in the United States (1966–2007) reveal it to be an exceedingly rare event, with only 22 documented cases. Risk factors for development of EO include higher Fitzpatrick skin types, extended duration of use, high concentration of hydroquinone, and, most importantly, use of hydroquinone without regular medical supervision. If EO is suspected, hydroquinone should be discontinued immediately [23], and the patient should be assessed for need of a skin biopsy.

Azelaic acid

Azelaic acid, which also works by blocking tyrosinase, has been used as an alternative to hydroquinone with the advantage that it can be used safely during pregnancy. In a randomized, double-blind multicenter study by Balina and Graup [24], 20% azelaic acid applied twice daily combined with broad-spectrum sunscreen was found to have similar efficacy

to 4% hydroquinone used twice daily combined with broad-spectrum sunscreen with regard to melasma size reduction, pigment intensity, and overall response after 24 weeks of treatment. Comparison of azelaic acid with hydroquinone 2% has not shown similar efficacy, with greater improvement seen in patients using 20% azelaic acid [25]. However, it should be noted that azelaic acid use has been associated with greater adverse skin reaction compared with hydroquinone in both studies.

Retinoids

Retinoids have also been used in treatment of melasma, and as monotherapy have moderate efficacy [26]. Retinoids are thought to treat hyperpigmentation through decreasing melanosome transfer, interrupting melanin synthesis, and inhibition of tyrosinase transcription [27,28]. In 2 randomized, double-blind, vehicle-controlled studies [29,30], patients showed significant improvement in melasma after 24 weeks of treatment with 0.1% tretinoin once daily together with SPF 15 sunscreen in both white [29] and African American patients [30]. Potential adverse effects include irritation, erythema, and skin dryness and flaking.

Combination creams

Triple-combination cream (TCC) containing hydroquinone, tretinoin, and steroid is currently the only hydroquinone-containing topical therapy to be approved by the US Food and Drug Administration (FDA) for treatment of melasma. In the 1970s, Kligman and Willis [31] reported success in treatment of melasma with their formula of 5% hydroquinone, tretinoin 0.1%, and dexamethasone 0.1%. The use of similar combination creams, including the combination of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinonide, have been studied and shown to be more effective in improving melasma not only compared with hydroquinone 4% cream alone [32], but with any of the TCC's agents in a dual-combination cream form [33]. Furthermore, in the latter study by Taylor and colleagues [33], the combination cream had a higher patient satisfaction compared with the hydroquinone group. Pretreatment with TCCs (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinonide) has also been advocated before laser treatment as a way to decrease melanin production before thermal injury [34]. The efficacy of combination creams has been attributed to the ability of tretinoin to enhance the penetration of hydroquinone as well as the ability of the corticosteroid to downregulate cellular metabolism

and melanin production while buffering tretinoin's potential irritative side effects [35].

ORAL THERAPY

Tranexamic Acid

Tranexamic acid (TA) is a synthetic derivative of lysine and, as a hemostatic agent, was FDA approved for heavy menstrual bleeding. Its use in the treatment of melasma was first reported in 1979. TA works by inhibiting the plasmin-plasminogen pathway. Increase in plasmin in keratinocytes leads to increase in production of arachidonic acid and alpha-melanocyte-stimulating hormone (alpha-MSH) production. Thus, by inhibiting the plasmin pathway, TA results in decreased melanogenesis [36].

Studies support the use of oral TA as an adjuvant therapy for in refractory cases of melasma or as a second-line or third-line agent [37], and there is some early evidence supporting the utility of oral TA as monotherapy [38]. Overall, randomized controlled trials have found that combination treatment regimens using oral TA as adjunct therapy results in greater reduction of melasma. This includes addition of oral TA to low-fluence quality-switched 1064-nm laser [39], TCC regimen [40], and hydroquinone [41]. Oral TA is commonly dosed at 250 mg twice a day. Studies suggest that the lightening effect is usually seen after 2 to 3 months of therapy [37,38]. In a retrospective analysis of 561 patients, Lee and colleagues [38] found that 89.7% of patients had documented improvement, 10% remained unchanged, and only 0.4% worsened. In general, patients who improved showed 50% improvement, with first sign of lightening occurring after 2 months of therapy. Based on current evidence in the literature, including a recent meta-analysis assessing the efficacy of TA, the risk of melasma relapse after discontinuation of TA remains high, suggesting TA therapy should not be short term [37]. Side effects of oral TA in general are considered to be rare and transient and include abdominal bloating, headache, and menstrual irregularities. However, a deep vein thrombosis was reported in a patient later found to have protein S deficiency [38]. Thus, clinicians should screen patients for both personal and family history of thromboembolic disease, stroke, and heart disease before starting oral TA therapy.

CHEMICAL PEELS

Chemical peels, both as monotherapy and in combination with other treatment modalities, have been used

for treatment of melasma due to their ability to increase epidermal remodeling and keratinocyte turnover [42]. Studies evaluating the efficacy of chemical peels, including alpha-hydroxy and beta-hydroxy acids, as monotherapy or in combination with other therapies for treatment of melasma in general have not shown consistent efficacy [26] with risk for dyspigmentation postprocedure.

Glycolic Acid Peels

Among chemical peels, glycolic acid is the one most extensively studied in treatment of melasma. Most studies evaluating serial glycolic acid peels (10%–70%), used as monotherapy or in combination with topical treatment, have not shown superiority over the use of topical therapy alone, including 2% to 4% hydroquinone [43,44] or tretinoin 1% [45]. Furthermore, compared with topical therapy alone, glycolic acid was associated with lower tolerability as well as posttreatment burning and ensuing hyperpigmentation [43,45].

Salicylic Acid Peels

Similar to glycolic acid, use of salicylic acid peels has not found to be more effective when compared with twice-daily use of 4% hydroquinone as monotherapy [46].

MICRONEEDLING

Microneedling, also known as collagen induction therapy, is a process involving repetitive puncturing of the skin with sterilized microneedles [47]. Although data from rigorous, large, well-controlled, placebo-controlled trials for use of microneedling in treatment of melasma are currently lacking, there is early evidence supporting its use in combination with depigmenting topical agents, including vitamin C, topical TA, and rucinol and sophora-alpha. In a split-face trial of 20 patients with melasma [48] with Fitzpatrick skin types III to V, combination of microneedling with 2 depigmenting topicals rucinol and sophora-alpha for 2 months resulted in a 9.9-point improvement on the Melasma Area Severity Index (MASI) Score compared with 7.1-point improvement in the topical treatment group alone. The study also showed a statistically significant increase in the average luminance value (L^*) in patients treated with skin needling and depigmenting serum (64.97) compared with patients treated with depigmenting serum alone (61.61). Another split-face study in 16 patients with recalcitrant dermal or mixed-type melasma demonstrated that combination of quality-switched neodymium:yttrium-aluminum-garnet laser (QS-Nd:YAG) followed

immediately by microneedling with vitamin C for 4 monthly sessions resulted in significantly lower mean MASI score with a better treatment response compared with the group treated with QS-Nd:YAG alone [49]. In another open-label study of 60 patients comparing effect of TA microinjections versus topical TA and microneedling at monthly intervals (0, 4, and 8 weeks) showed better improvement in MASI scores in patients treated with microneedling (35.72% improvement in the MASI score in the microinjection group compared with 44.41% improvement in the microneedling group at the end of the third follow-up visit); however, this difference was not statistically significant [50]. In a retrospective analysis of 22 patients with resistant melasma, Lima [51] showed patient satisfaction and improvement of melasma in 100% of patients who had received microneedling followed by triple-combination (0.05% tretinoin + 4% hydroquinone + 1% fluocinolone acetonide) and an industrialized tinted sunscreen with SPF 60, but there was no control arm in the study.

Despite some of the improvements seen in the previously described studies, there are currently no prospective, well-controlled randomized studies comparing the efficacy of microneedling technique to traditional well-established therapies in melasma, including hydroquinone and TCCs. The improvements in melasma seen these studies are likely the result of enhanced penetration of the topical depigmenting agents by microneedling, rather than the ability of the microneedling to cause significant epidermal or pigment turnover on its own. Thus, microneedling, if used, should be used in combination with other treatment modalities, such as topical depigmenting agents along with strict photoprotection. Additionally, attention should be paid to not cause excessive trauma during the procedure to avoid PIH and the potential worsening of melasma [51].

ENERGY-BASED TREATMENTS

Nonablative Lasers

Nonablative infrared fractional lasers including 1540-nm, 1550-nm, and 1927-nm lasers have all been used in treatment of melasma. Nonablative fractional lasers create microscopic zones of coagulated thermal tissue injury known as microscopic treatment zones amidst a background of intact skin. The proximity of uninjured skin allows basal keratinocytes to migrate across the fractional zones of injury and aid in the healing process. The damaged zones of coagulated tissue (including damaged melanin) are then eliminated

through the skin surface. Although compared with ablative lasers, nonablative lasers induce less injury to the skin and hence generally avoid many of the side effects associated with those devices, their use in melasma has not produced consistently effective results.

1550-nm Fractional Laser

A randomized control trial of 20 Korean patients [52] (Fitzpatrick skin types II–V) evaluating the efficacy of biweekly nonablative 1550-nm fractional laser treatments for 8 weeks compared with TCC (hydroquinone 5%, tretinoin 0.05%, triamcinolone 0.1%) found no difference between the groups with regard to either improvement or worsening of melasma. At the 6-month follow-up, multiple patients in both groups experienced recurrence and a significantly higher number of patients preferred the topical. Similar results were seen in a randomized controlled split-face study [53] of 29 patients with melasma comparing 1550-nm nonablative fractional laser with once-daily triple-combination therapy (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1% cream) for 15 weeks. Mean patient global assessment, patient satisfaction, physician's global assessment, melanin index, and lightness (L-value) were significantly lower for the laser treatment side. Again, a significant portion of the patients experience PIH (31% of patients) posttreatment, and at the 6-month follow-up visit, patients preferred the side treated with triple-combination therapy.

1927-nm Fractionated Nonablative Thulium Laser

The 1927-nm fractional nonablative laser has a higher absorption coefficient for water and a greater capacity to alter epidermal processes including hyperpigmentation [54]. In a nonrandomized pilot study of 14 patients treated with 1927-nm nonablative fractional laser and 4% hydroquinone, Polder and Bruce [54] showed an improvement of 51% in MASI score at 1-month follow-up. This subsequently dropped to 34% at the 6-month follow-up visit. The mean improvement in melasma at 6-month follow-up by blinded evaluators was mild. Although the study was not randomized or controlled, the treatment was safely used in patients with Fitzpatrick skin type I to IV without any incidence of PIH, hypopigmentation, or scarring from treatment. In a prospective, nonrandomized study of 20 patients [55] (mainly with Fitzpatrick skin types I–III and 1 with Fitzpatrick skin type IV) showed an average moderate improvement at 1-month follow-up and mild to moderate improvement at

3-month follow-up using blind assessment of standardized facial imaging photographs.

Overall, current evidence suggests that despite the relative safety of nonablative fractional lasers in treatment of melasma (given that nonaggressive protocols using low fluences are used), their use at best results in mild to moderate improvement of melasma with the improvement generally dropping off at longer follow-up (ie, 6 months) evaluations. Furthermore, results are not superior to use of triple-combination therapy and in fact there is a significant risk of rebound melasma, or PIH with use of 1550-nm nonablative lasers.

Low-Energy, Low-Density 1927-nm Fractionated Nonablative Diode Laser

In contrast to the high-energy, high-density, 1927-nm nonablative fractionated thulium lasers, Clear and Brilliant Permea fractionated nonablative laser (Solta, Bothell, WA) delivers a low-fluence and low-density energy with a broader safety profile in treatment of melasma. In a single-center nonrandomized study [55] of 23 women with Fitzpatrick skin types I to VI (11 with diagnosis of photodamage, 10 with melasma, and 2 with PIH) who received 4 to 6 treatments with Clear and Brilliant Permea fractional 1927 diode laser (energy of 5 mJ, and 5%–10% treatment coverage, up to 8 passes), blinded physician assessment of 20 subjects revealed an average of moderate improvement, and 55% of subjects reported a marked to very significant improvement at the 1-month and 3-month follow-up visits. Of note, the investigators reported a transient perioral PIH in 1 Asian subject with melasma (Fitzpatrick skin type IV), which resolved 2 months after study completion.

Although well-controlled, randomized studies comparing the efficacy of Clear and Brilliant to standard topical therapies are currently lacking, this study, as well as our own clinical experience, support the use of this laser as a safe and mild to moderately efficacious treatment for melasma in all skin types.

Fully Ablative Lasers

Fully ablative lasers using carbon dioxide (CO₂), erbium:YAG, and yttrium scandium gallium garnet (2790 nm) wavelengths were developed to resurface skin by ablating rather than coagulating zones of skin tissue. These lasers induce a much higher degree of tissue injury with longer recovery times. When compared with fractional nonablative lasers, they have a higher risk for adverse events, including PIH, rebound

melasma, and even scarring. Thus, their use in treatment of melasma is not recommended.

Fractional Ablative Lasers

In contrast to fully ablative lasers, fractional ablative carbon dioxide and erbium:YAG lasers have shown safer and more effective results. In a study of 30 female patients with Fitzpatrick skin type II to IV, Trelles and colleagues [56] compared efficacy of the Kligman formula (group A) with fractional ablative CO₂ laser (UltraPulse Active FX) using high power, fixed pulse width, and low frequency (group B) compared with both laser and maintenance topical cream containing kojic acid, glycolic acid, and hydroquinone 2% (group C). At 1 month, satisfaction index and overall efficacy in groups A, B, and C were 100% in all groups, but this efficacy dropped off in further follow-ups in all but the combination group (C). The combination group not only maintained patient satisfaction and overall efficacy, but showed significant improvement in MASI scores at the 6-month and 12-month follow-ups. In a randomized controlled, split-face study comparing fractional CO₂ laser treatments with low-fluence QS-Nd:YAG in 40 patients with Fitzpatrick skin types II to IV, Jalaly and colleagues [57] showed a greater reduction in melanin index and modified MASI (mMASI) score in the side treated with fractional CO₂ at the 2-month follow-up. Neither group experienced any adverse effects; unfortunately, however, longer follow-up data was not provided for either group.

Intense Pulsed Light

Intense pulsed light (IPL) generates a noncoherent, high-energy, broad-spectrum light in the range of 500 to 1200 nm, using a flashlamp. This energy (with or without filters to increase target specificity) can be absorbed by melanin in keratinocytes as well as melanocytes in the skin, allowing IPL to be used in treatment of melasma. Multiple studies have evaluated IPL as monotherapy or in conjunction with other therapies. Results from randomized controlled studies highlight that combination of IPL and topical therapy (either hydroquinone or TCC) is more effective than either treatment alone, and can result in melasma improvement.

A randomized, single-blinded open-label study of 62 patients (Fitzpatrick skin types II to V) with melasma refractory to TCC [58] showed that a single IPL treatment with a filter of 560 nm and fluences ranging from 12 to 22 J combined with TCC resulted in a 49.4% reduction of MASI score at 6 months compared

with no change seen the group using TCC alone. Unfortunately, the study did not outline the detailed parameters used for IPL or the frequency of TCC application. Superiority of TCC and IPL was also highlighted by a split-face randomized study [59] that showed that patients receiving a combination of TCC and IPL saw greater improvement of melasma, by subjective investigator assessments, compared with those receiving a placebo cream and IPL.

Combining IPL with hydroquinone also has shown greater efficacy in melasma treatment compared with use of hydroquinone alone. In a randomized study in which the treatment group received 4% hydroquinone, sunscreen, and monthly IPL treatments for 4 months, Wang and colleagues [60] showed greater improvement in relative melanin index compared with the control group that used only used hydroquinone and sunscreen. Recurrence was, however, seen in 2 patients.

Recent evidence suggests that low-fluence, short-pulse duration IPL protocols [61] can be an effective therapy in improving melasma with minimal side effects. Studies suggest that minimum of 4 treatments may be necessary to see good improvement.

Overall, results from randomized studies and our own experience show that used judiciously and at relatively low fluence, IPL can be an effective treatment for melasma, and combination with topical therapy (hydroquinone 4% or TCC) enhances the efficacy and durability of the results.

Pulsed Dye Laser

Given the recent advances in our understanding of melasma's vascular component, pulsed dye lasers (PDLs) have begun to be used as a treatment modality. In a prospective, randomized, single-blind, split-face study, Passeron and colleagues [62] compared efficacy of PDL (3 sessions at weekly intervals) plus TCC (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%, Tri-Luma cream) applied daily for 4 months compared with TCC alone. For each PDL treatment, 2 passes were used: 1 using settings for treatment of hyperpigmentation followed immediately by a second pass with settings aimed at treatment of the vessels. Both groups used sunscreen with SPF of 50 or higher. One-month follow-up results showed a greater improvement of melasma and patient satisfaction in the combination group (PDL and TCC), but this improvement was seen only in patients with Fitzpatrick skin types II and III. Half of the patients with Fitzpatrick skin type IV, who received the treatment, unfortunately experienced PIH and their melasma did not improve.

The investigators of the study attributed the PIH to the PDL pass targeting melanin clearance, and thus recommended avoidance of this specific passage in future studies, and using only settings that target the vascular component. Interestingly, 3 years after the completion of the study, 1 patient presented with melasma recurrence that completely spared the skin area previously treated with PDL, suggesting that treatment of the vascular component may prevent recurrence [63].

In a retrospective analysis of 11 patients with Fitzpatrick skin types II to IV whose melasma exhibited subtle or subclinical telangiectatic erythema identified by spectrophotometry, and who had been treated with PDL followed by 1927-nm fractional low-powered diode laser (Clear and Brilliant Permea; Solta) 15 minutes later, 54% of patients demonstrated a greater than 50% improvement in melasma presentation [64]. The PDL settings used were those targeting telangiectasia: 10-mm spot, 10 to 20-ms pulse duration, and 7.5 to 8.5 J/cm² fluence. There was no report of adverse events.

Much has yet to be deciphered about the vascular phenomenon in melasma and how it relates to the pathogenesis, treatment, and potential recurrence of melasma. Unfortunately, data from randomized controlled studies are currently lacking. However, results from these initial studies suggest that PDL, as an effective vascular targeting agent, may be used in the armamentarium of melasma treatment, not as monotherapy for pigment clearance, but in conjunction with other melanin-targeting agents, both to enhance melasma clearance and potentially prevent its recurrence.

Quality-Switched Lasers

Quality-switched (QS) lasers, including QS ruby lasers and QS-Nd:YAG, have been used in the treatment of melasma. Given that melanosomes have thermal relaxation times in the range of 50 to 500 nanoseconds, these lasers can not only target melanosomes by delivering short pulses in the nanosecond range, but cause its destruction through a photoacoustic effect [10,65].

Q-Switched Ruby

The use of Q-switched ruby (694 nm) laser remains controversial. Earlier studies [66,67] reported that use of the laser for melasma was ineffective and often resulted in worsening hyperpigmentation. Recent studies, however, have presented more promising results using fractional QS ruby laser [68–70]. Similar to lessons learned from studies using QS-Nd:YAG lasers, more safe and effective protocols include multiple treatments with lower fluences of energy. Hilton and

colleagues [68] saw PIH and/or recurring melasma in 28% and 44% of their patients, respectively, using higher fluences (4–8 J/cm²) per session compared with Jang and colleagues [69] who used fluences of 2 to 3 J/cm² and found no incidence of dyspigmentation or other long-term adverse effects posttreatment in any of the treated patients.

Q-Switched Neodymium:Yttrium-Aluminum-Garnet Laser

Growing evidence has shown significant potential and efficacy for melasma treatment using low-fluence QS-Nd:YAG lasers. This laser not only can be safely used in all skin types, but can penetrate to the deep dermis (without creating significant epidermal damage.) It can selectively target and destroy dermal melanosomes at low fluences without causing melanocyte death through a process known as subcellular-selective photothermolysis [71,72]. Targeting melanosomes without causing collateral damage to surrounding tissue and melanocytes is important, as it lowers the risk of postinflammatory pigmentary change so commonly seen after melasma laser treatment, including both hypopigmentation and hyperpigmentation.

Yet, despite evidence supporting efficacy of low-fluence QS-Nd:YAG in treatment of melasma, “low-fluence” treatment protocols are not standardized. Furthermore, many of the previously reported parameters, which initially appear effective, have been complicated by frequent and early melasma recurrence [73–75], PIH [75,76], and punctate leukoderma [74–76]. The protocols in these studies used higher fluences (>2 and up to 4 J/cm²), frequent treatment sessions (weekly), and/or higher number of passes (up to 20).

Uniquely, the study published by Kauvar [77] demonstrated the highest treatment success, not only by reporting a high rate of melasma improvement in her patient cohort, but also the maintenance of this improvement at 6-month and 12-month follow-up without any adverse effects. Her method involved a combination approach of microdermabrasion, low-fluence QS-Nd:YAG, and topical 4% hydroquinone for treatment of melasma in 27 female patients with refractory melasma. In her study, more than 80% of patients experienced more than 76% improvement in melasma at 3-month, 6-month, and 12-month follow-up. Furthermore, unlike other studies, there was no report of swelling, crusting, blistering, PIH, or guttate leukoderma in any of the patients. The success of her results has been attributed to the combination

approach using microdermabrasion to increase the laser penetration and daily topical regimen to inhibit melanogenesis [78]. As previously noted, the combination approach has been documented to be both superior and safer compared with monotherapy alone. Additionally, lower fluences of $\leq 2 \text{ J/cm}^2$ delivered with less-frequent treatment intervals used in the Kauvar [77] protocol have been shown to be safer with fewer side effects compared with other published protocols [79–81]. Despite this success, the results of the Kauvar [77] study have been questioned due to its observational nature and the lack of a controlled trial to confirm the benefits.

Lessons from these studies have highlighted the importance of protocols using lower fluences (usually $\leq 2 \text{ J/cm}^2$), lower number of passes (2 or 3 compared with 10 or 20 used in some studies), delivered with less frequency (monthly rather than weekly) to avoid treatment-related adverse events.

Picosecond Lasers

Picosecond lasers have introduced a novel method for pigment fragmentation by delivering energy at a speed that is potentially 3 orders of magnitude faster than the nanosecond speed of QS lasers. It is thought that this faster mode of energy delivery can result in a “cleaner” mode of melanosome fragmentation and clearance by causing injury that is more acoustically driven and has less damaging photothermal effects. Thus, in theory, with these lasers, adjacent tissue suffers less thermal damage and melanosomes are shattered into smaller particles that are more efficiently cleared by the macrophage system. Picosecond lasers are currently available with laser outputs of 532 nm, 755 nm, and 1064 nm. A recent randomized split-face study of 39 Korean patients by Choi and colleagues [82] using a picosecond dual-wavelength 595-nm and 1064-nm laser in combination with 2% hydroquinone versus hydroquinone 2% alone showed superior improvement in relative lightness value at completion of the trial and follow-up period for the laser-treated side, but no difference in mMASI scores or patient satisfaction for the laser-treated group during the follow-up period, indicating likelihood of melasma recurrence after treatment cessation. So, although picosecond lasers have potential to improve melasma treatment outcomes, much still needs to be deciphered about their efficacy and safety.

SUMMARY AND DISCUSSION

The pathogenesis of melasma is complex and not yet fully understood. Interplay between hormones and environmental factors, including UV and visible light,

in the setting of genetic predisposition leads to melanocyte hyperactivity and increased angiogenesis. This clinically manifests as a hyperpigmentation disorder that is difficult to treat and generally requires a multimodality treatment approach. The goal for effective treatment of melasma includes removal of the excess melanin in the epidermis and dermis, as well as suppression of further melanogenesis. Without these 2 steps, there is high risk for relapse of melasma after treatment. Despite the wide array of high-technology energy and light-based devices available today, the gold standard for first-line treatment of melasma remains topical therapy using strict photoprotection with broad-spectrum sunscreens and either hydroquinone 4% cream, tretinoin, or TCCs. If a patient is not responding to topical therapy, addition of laser treatments can be recommended using low-fluence QS-Nd:YAG (first line), or fractional nonablative resurfacing (second line), given that these are the laser devices that when used judiciously, studies have shown to not only be safe and effective in melasma treatment, but provide a clearance benefit beyond that seen with use of topical therapy alone. It is important to counsel patients to continue their use of photoprotection and a topical lightening agent following laser treatment to reduce the risk of melasma recurrence.

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Picosecond Lasers

Do the Data Support the Claims?

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KEYWORDS

• Picosecond laser • Fractional picosecond • Diffractive lens array • Tattoo

KEY POINTS

- Laser tattoo removal requires many treatments, and results can be variable and oftentimes disappointing.
- Shorter pulsed, or picosecond pulsed, lasers have been developed to deliver spatially confined thermal and high photoacoustic energy in order to effectively and safely treat tattoos and pigmented lesions.
- Picosecond lasers deliver enhanced efficacy for the treatment of tattoos and pigmented lesions when compared with the older 40- to 50-nanosecond devices.
- The fractional delivery with the picosecond devices has opened up a new method of rejuvenation for photodamaged skin and the treatment of scars.

INTRODUCTION

The term “tattoo” is derived from the Tahitian word “tattau,” which means “to mark” [1]. The tattooing of skin is the procedure in which pigment granules are permanently implanted into the dermis. Tattoos can be cosmetic (decorative tattoos or permanent makeup), therapeutic (markers during radiation therapy, camouflage for vitiligo, or areola reconstruction after mastectomy), or accidental (exogenous impregnation of particles after cutaneous abrasion) [1]. In western culture, cosmetic tattoos have become an increasingly common form of personal expression, mirroring the increased prevalence of tattoos in popular culture. As times and fashions change, tattoos serve as permanent reminders of temporary fads and may inflict significant social and psychological distress on the tattooed individual. As such, the demand for tattoo removal has increased; however, the intended permanence of the

ink in the skin poses a challenge to its removal. Nonspecific destructive methods, such as excision, salabrasion, dermabrasion, and ablative carbon dioxide (CO₂) lasers, can result in significant scarring and a final appearance less attractive than the original tattoo. Therefore, short-pulse lasers were developed in order to precisely and safely target tattoo particles. In this review, the authors discuss the evidence, application, and limitations of picosecond lasers in the treatment of tattoos as well as their future applications in fractionated form in the rejuvenation of damaged skin.

BASIC PRINCIPLES OF TATTOO REMOVAL

In order to analyze the evidence behind picosecond laser tattoo removal, a discussion of tattoo pigment particles is essential. India ink is a common pigment used in tattoos. With the use of various needling techniques,

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ink is mostly implanted in the papillary and reticular dermis. Several days after placement, the ink is phagocytosed by macrophages and histiocytes, which then migrate toward the dermal perivascular zones. In these cells, the ink particles, generally 40 to 100 nm in diameter, are loosely packed in granules that are 400 to 4000 nm in diameter. Therefore, the ink could be targeted as granules as large as 4000 nm to particles as small as 40 nm.

The laser treatment of tattoo particles uses 2 mechanisms. The photothermal mechanism suggests that the pigment absorbs the laser energy and fragments into smaller particles. Given the theory of selective thermolysis, the laser pulse duration is ideally less than or equal to the thermal relaxation time of the particle, which is proportional to its size [2]. The photoacoustic mechanism posits that the laser beam generates strong acoustic waves within the pigment particle, leading to its breakup [3]. Therefore, shorter pulsed lasers have been developed with the intention of delivering pulses short enough, yet powerful enough, to treat minute pigment particles while spatially confining heat and decreasing adverse events.

The quality-switched (QS) Ruby (694 nm), QS Nd:YAG (1064 nm), and QS Alexandrite laser (755 nm) were developed in the 1990s and deliver energies in the nanosecond range. These lasers provide a practical and affordable method to remove tattoos with minimal downtime and side effects. The pulse durations of these devices can range from 5 to 100 nanoseconds. All 3 wavelengths are absorbed by black ink. The Ruby and Alexandrite lasers are also absorbed by green and blue ink. The frequency-doubled Nd:YAG (532 nm) laser targets red and yellow ink. The energy required to achieve adequate clearance can result in undesirable side effects when used in the nanosecond domain. As ink particles decrease in size with treatment, pulse durations in the nanosecond range can lead to unnecessary overdelivery of heat and therefore increase transfer of heat to surrounding tissue. Excess heat can result in scarring and hypopigmentation. Furthermore, complete clearance of professional heavily inked tattoos is difficult to achieve. Even with pulses in the nanosecond domain, there is a significant difference in the pulse durations between a 5-nanosecond and a 50-nanosecond device (10 times shorter at 5 nanoseconds); the shorter pulse duration theoretically results in tighter thermal confinement and less unwanted side effects.

The utility of pulse durations shorter than those in the nanosecond domain was described by Jacques [4]. It was theorized that picosecond or femtosecond pulses would

not only rapidly deliver heat that is spatially confined within small ink particles but also briskly deliver higher acoustic energy than nanosecond lasers and thereby inflict increased tensile strength leading to fragmentation of the tattoo particles. Experimental picosecond and femtosecond devices in animals and later in humans corroborated this theory and demonstrated successful tattoo clearance with these devices [5,6]. These findings eventually led to the development of commercial lasers delivering energies with picosecond pulse widths. Modeling data by Ho and colleagues [3] suggested that a pulse duration of 10 to 100 picoseconds would be ideal to treat graphite ink particles.

PICOSECOND LASERS AND TATTOOS: THE EVIDENCE

The first commercial picosecond laser developed was an Alexandrite laser manufactured by Cynosure with a pulse duration of 750 picoseconds. In one study, Saedi and colleagues [7] showed at least 75% clearance of blue and black tattoos using the 755-nm Alexandrite picosecond laser after an average of 4.25 treatments. In another study, this laser demonstrated rapid clearance of blue and green ink, pigments that had previously been notoriously difficult to clear with many treatments with the 40- to 50-nanosecond Alexandrite lasers [8]. This study demonstrated greater than 75% clearances after 1 to 2 treatments with two-thirds of patients achieving complete clearance with fluences of 2.0 to 2.83 J/cm² [8]. Clinicians could now offer patients greater clearance of multicolored ink, in just a few treatments and with minimal side effects (Figs. 1 and 2).

In 2012, this picosecond Alexandrite laser (Picosure, Cynosure, Westford, MA) was compared with 2 commercially available nanosecond devices: the Alexandrite laser (Accolade, Cynosure, Westford, MA at 50 nanosecond) and an Nd:YAG 1064/532-nm (RevLite, Cynosure, Westford, MA at 5 nanosecond) [9]. The picosecond device exhibited similar clearances in comparison to the other 2 devices operating at the manufacturer's suggested optimal treatment parameters with half the number of treatments and at significantly lower fluences.

In a study performed by Pinto and colleagues [10], a 450-picosecond 1064-nm Nd:YAG laser was compared with a 5-nanosecond 1064-nm Nd:YAG. Results demonstrated no significant difference after 2 treatment sessions in previously treated tattoos. However, only 2 treatments were administered, and the utility of shorter picosecond pulses in clearing tattoos truly becomes apparent after several treatments, when ink particles are much smaller

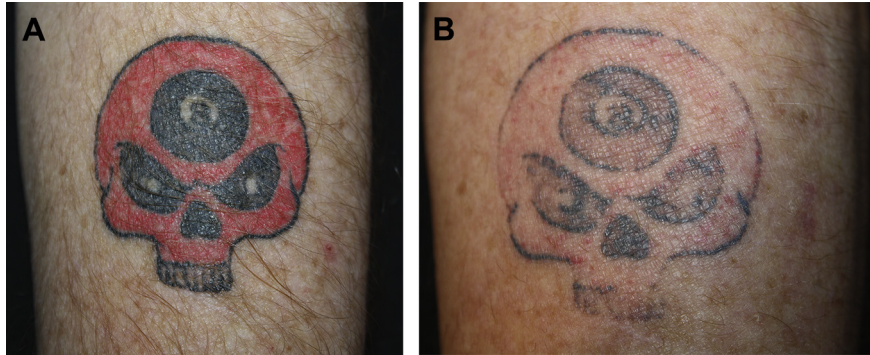


FIG. 1 (A) Red and black tattoo before laser treatment. (B) Significant clearance of red and black pigment after 6 treatments with 755-nm picosecond Alexandrite laser.

in size. In another study by Kono and colleagues [11,12] that was conducted with the 450-picosecond 1064-nm Nd:YAG laser and a 50-nanosecond Nd:YAG laser, the picosecond device offered greater clearance of black pigment after 4 treatment sessions. Another commercially available picosecond 532/1064-nm Nd:YAG laser (Enlighten, Cutera, Brisbane, CA) offers a 2-nanosecond pulse duration as well as a 750-picosecond pulse width option. The longer pulse width should be used for heavily inked tattoos early in the treatment phase, and as particles decrease in size with subsequent treatments, the shorter picosecond pulse duration would theoretically offer further clearance. These data suggest that the picosecond lasers are an improvement over the longer-pulse nanosecond lasers, especially as the ink particles diminish in size with subsequent treatments, and that 755-nm

picosecond devices may be more effective than nanosecond lasers in the treatment of blue and green ink. Picosecond lasers also enable clinicians to treat tattoos at significantly lower fluences than nanosecond devices with less discomfort and less heat transfer to surrounding tissue. From a practical view, a picosecond device may not deliver dramatically greater clearance of tattoos in comparison to 2- to 6-nanosecond devices. However, the authors' experience and the data from the literature suggest that picosecond lasers do offer a significant difference in results in comparison to 40- to 50-nanosecond devices.

CHALLENGES TO THE TREATING TATTOOS

Many factors render the successful treatment of tattoos challenging. One major issue is that there is no standard pigment universally used in tattoos. In addition, the process of injecting the ink into the skin is not standardized. In Europe, through legislation passed by the European Union, an index displaying which substances are not to be used in tattoo dyes exists. In the United States, a comparable list has not been developed.

In the placement of tattoos, various methods and needles of varying sizes, grinds, and thicknesses may be used, affecting the size and depth of the ink deposited in the skin. With a special tattoo gun, the artist can adjust the frequency and depth of skin penetration. The pressure applied onto the skin and the retention time of the needle at a specific location also determine the amount and depth of ink placed into the skin. Aftercare also affects the amount of ink retained within the skin: improper aftercare can lead to incomplete pigment retention, infection, and scar formation. Most tattoo artists, as well as their clients, are unaware of the exact contents of the color being used. Tattoo dyes consist of binders, solvents, and other excipients in addition to the pigment particles. The ink

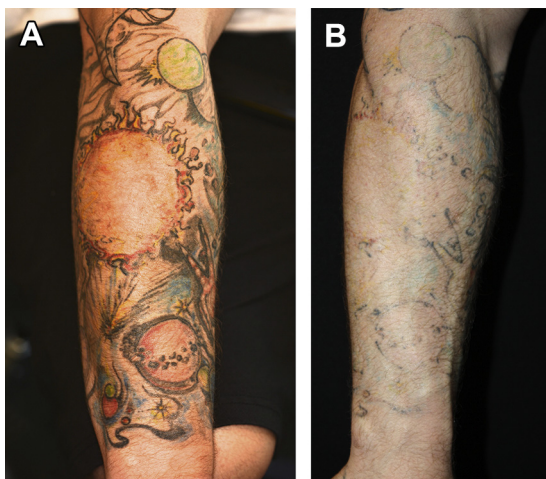


FIG. 2 (A) Multicolored tattoo before laser treatment. (B) Significant clearance of tattoo after 6 treatments with 755-nm picosecond Alexandrite laser.

particles as well as the excipients play significant roles in how the tattoo will integrate and interact with the skin, and likely how it would respond to laser treatment.

APPLYING THE EVIDENCE AND TREATING THE PATIENT

Pretreatment Planning

In order for the clinician to offer a comprehensive tattoo removal service that would effectively treat most colors and a wide variety of patients, the clinic is best configured for success with an Nd:YAG and an Alexandrite or Ruby laser. Before initiating any treatment, the clinician should discuss realistic expectations at length with the patient. Before embarking on laser tattoo removal, the patient must fully be aware that the road to acceptable clearance can be a long, arduous, and costly journey. Several treatment sessions are necessary, and treatment response is often variable.

When first assessing the patient, the clinician should inquire if a professional artist or an amateur tattooist placed the tattoo. Professional tattooists tend to be more precise with the amount of pigment placed into the skin and depth of placement. Knowledge of the age of the tattoo is also crucial. Because of slow degradation of tattoo particles over time and subsequent phagocytosis by macrophages and other inflammatory cells, older tattoos tend to fade over time and may require less treatment sessions. Furthermore, it is important to determine if the tattoo is a cover-up over an older preexisting tattoo. Cover-up tattoos often contain densely and deeply packed pigment of varying overlaying colors and particles, often making these tattoos much more difficult to treat.

Before treatment of the entire tattoo, and if several wavelengths are available, test spot squares of 1 cm² (1 cm × 1 cm) should ideally be administered using different wavelengths and fluences. Manufacturer's recommended settings are often acceptable starting points when treating a naive tattoo; however, caution should still be exercised. Gentle tattoo whitening with minimal epidermal change should serve as the clinician's end point for the test spots as well as the entire tattoo. Four weeks later, the test spots would be assessed and the most effective wavelength would be used to treat the tattoo in its entirety.

Treatment and Posttreatment Care

Because each patient has a different threshold for pain, the methods of obtaining adequate anesthesia will vary from patient to patient. Patients with higher

thresholds for pain and with tattoos in less sensitive locations may only require 45 to 60 minutes of topical anesthesia before treatment. Of note, topical anesthesia does not alter the penetration of light through the skin; however, the skin should still be thoroughly wiped before treatment. In addition to topical anesthetics, forced cool air can provide further anesthesia and comfort during the procedure. In patients who require more anesthesia, local infiltration of lidocaine can reduce pain, and the addition of epinephrine can help diminish bleeding.

After adequate anesthesia is achieved, the tattoo is treated with the appropriate wavelength and fluence that achieves marked whitening of the tattoo, but with minimal epidermal crusting, bleeding, and tearing. One pass is usually sufficient; however, waiting 20 to 30 minutes after the first pass or the use of a protective perfluorodecalin-infused patch may allow the administration of a second pass [13]. After treatment, the tattoo is generously coated with a hydrating petrolatum jelly and covered with a nonadhesive dressing. After 24 hours, the patient is to wash the tattoo twice daily with a gentle cleanser and apply petrolatum jelly after each wash until healed.

In general, treatment is administered at 4-week intervals. However, longer time intervals in between sessions may allow for continued immunologic removal of tattoo ink during the healing process and further clearing with each treatment.

INNOVATIONS AND FUTURE DIRECTIONS: THE FRACTIONATION OF PICOSECOND PULSES

During the development of the picosecond Alexandrite laser, the clinical commercial lead at Cynosure, Marina Kamenakis, posited the idea to deliver picosecond energy with a diffractive lens array for the treatment of cutaneous pigmentary disorders and for facial rejuvenation. The scientific team had previously developed a similar lens array for nonablative treatments and was open to this idea. Initially met with skepticism, it soon became clear that there were visible improvements in skin pigmentation, texture, pore size, and even wrinkles with this laser and hand piece.

This diffractive lens is made up of individual lenses arranged in an array with 500-μm center-to-center spacing, which when used with a 755-nm picosecond Alexandrite laser produces fractional high-energy zones where 70% of the energy is delivered into these areas with the rest of the energy delivered over a low fluence background (Fig. 3). These high-energy zones are

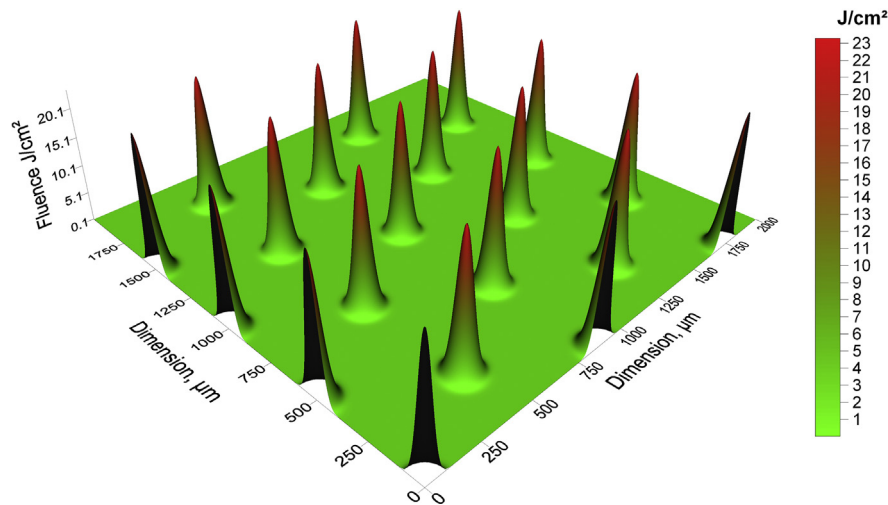


FIG. 3 Fluence distribution in the treatment plane on the skin surface. Treatment spot size 6 mm; peak fluences are 23 J/cm², and average fluence setting 0.71 J/cm². (From Tanghetti EA. The histology of skin treated with a picosecond Alexandrite laser and a fractional lens array. *Lasers Surg Med* 2016;48:647; with permission.)

focused onto the skin surface. Melanin is the first significant chromophore that this narrow focused laser light encounters. The absorption of 755-nm light by this molecule appears to eject a seed electron, which grows in an avalanche process during the laser pulse. Irradiation by this laser produces a small plasma ball, which rapidly generates a small steam bubble (Fig. 4). This very localized injury can be seen histologically as a discreet vacuole with very little injury to the surrounding keratinocytes. Over the next 24 hours, these vacuoles become rehydrated and fill with cellular debris, which stain positively for melanin (Fig. 5). Tanghetti [14] using a confocal microscope demonstrated that these injury zones correspond to the grid of the diffractive lens array produced by this laser.

Numerous clinical studies were undertaken to validate the initial clinical observations of efficacy. Brauer and his colleagues [15] demonstrated improvement in acne scars with the fractional picosecond Alexandrite laser. It was particularly notable that darker skin types were included in this study with excellent outcomes. Subsequently, Dr Roy Geronomeus' team in New York performed a study exclusively in darker skin types IV, V, and VI with multiple passes and multiple sessions using this diffractive array with good outcomes and without the postprocedural dyspigmentation seen with other ablative devices [16]. In Asia, studies demonstrated improvement in tone, texture, pore size, and pigmentation [17]. The

popularity of this type of high-energy fractional picosecond treatment in Asian skin appears to be because of the minimal downtime and the absence of postprocedural dyspigmentation associated with treatments. The skin lightening associated with the production of laser-induced optical breakdown (LIOBs) in the epidermis and the reduction of pigment due to the targeting of melanin are appealing in this region of the world.

In the United States, McDaniel [18] demonstrated the utility of treatments with the picosecond Alexandrite laser with the diffractive lens array in patients with photodamage. He showed significant improvement in fine wrinkles, mottled hyperpigmentation, lentigines, skin tone, and texture. Four to 5 treatments are generally required for significant improvement. He demonstrated in a series of photographs the mild postprocedural erythema lasting for a few hours (Fig. 6). This redness lasts for a few hours and can be easily concealed with makeup. There is mild discomfort associated with these treatments sometimes requiring a topical anesthetic.

In areas off the face, the picosecond Alexandrite laser with the fractional optic has been used as a rejuvenation tool. Areas, such as the upper chest and the neck that are sensitive and prone to scarring, have shown significant improvement with this device [19,20]. Improvements of dyspigmentation, wrinkling, texture, and fine scarring have been

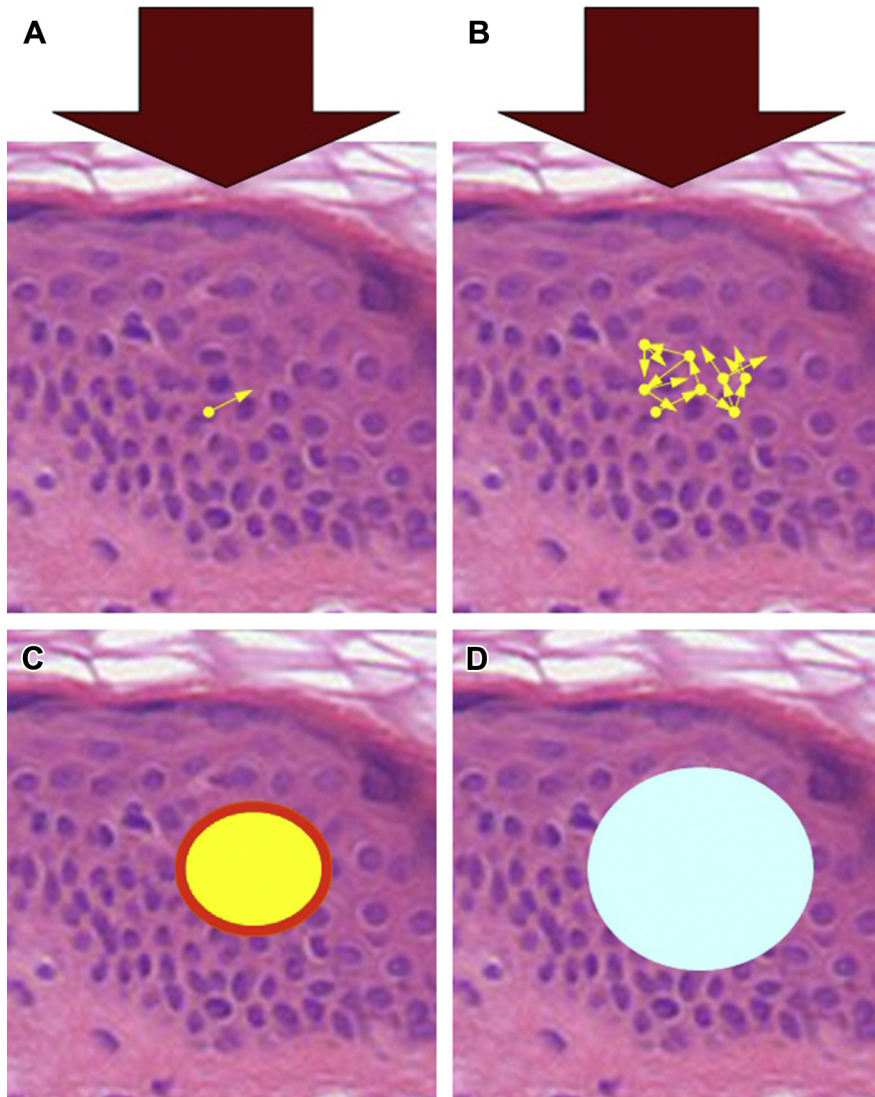


FIG. 4 Process of vacuole formation in the epidermis. **(A)** A high-intensity portion of the laser beam (arrows) created by the diffractive lens array irradiates a region of the skin. A seed electron is ejected from an absorber (melanin). **(B)** The number of free electrons grows in an avalanche process. Electron plasma density increases absorbing energy from the beam. **(C)** The laser beam terminates leaving a hot plasma ball. The plasma ball rapidly heats the surrounding tissue above boiling temperature. **(D)** Steam expansion creates a vacuole in the epidermis. (From Tanghetti EA. The histology of skin treated with a picosecond Alexandrite laser and a fractional lens array. *Lasers Surg Med* 2016;48:651; with permission.)

demonstrated after a series of treatments. In another area, the hands, Saluja [20] has reported improvement in sun damage with reduction of dyspigmentation and improvement in texture and wrinkling (Fig. 7). These reports and the experiences in clinics

throughout the world have demonstrated the safety and efficacy of this device in the treatment of many conditions in a variety of anatomic areas.

The benefits of these treatment protocols with the picosecond Alexandrite laser with the diffractive lens

755 nm 0.71 J/cm² MI 19 ST III



FIG. 5 Intraepidermal vacuoles at 24 hours after treatment with a picosecond Alexandrite at 755 nm and a diffractive lens array.

array appears to result from the production of collagen, elastic tissue, and mucin in the dermis, which can be seen after a series of treatments [15]. Because the only histologic findings of a change in the skin are the epidermal vacuoles, the authors have postulated that the production of these LIOBs is responsible for a robust reparative response with the production of cytokines, chemokines, and other growth factors. It should not be totally unexpected that dermal remodeling can occur in the absence of dermal wounding. Kang has reported improvement in longstanding older acne scars with the use of a topical retinoid, adapalene (0.3%) [21]. This drug

appears to stimulate epidermal and dermal remodeling without wounding.

After the success of the picosecond Alexandrite laser with the flat optic and the diffractive lens array, competition in the marketplace produced a family of picosecond Nd:YAG lasers for tattoo removal that also came with holographic optics and various lens arrays, which were able to deliver light in a fractional manner. In an attempt to better understand these different technologies, Tanghetti [22] studied the clinical cutaneous findings and histologic results immediately after treatment and at 24 hours with the picosecond 523-nm, 1064-nm, and 755-nm lasers with a diffractive lens array. These studies were later repeated with a picosecond 532 nm and 1064 nm with a holographic optic in comparison to the picosecond Alexandrite laser with the diffractive lens array. The holographic optic and diffractive lens arrays with the 2 Nd:YAG wavelengths both produced epidermal vacuoles, but also produced microscopic zones of hemorrhage. Clinically, this resulted in superficial hemorrhage immediately after treatment that was still present, especially at the higher energies, 24 hours later. The Nd:YAG-induced erythema and hemorrhage differed from the erythema that is short-lived without hemorrhage at 755 nm with the diffractive lens array [23].

These investigations suggest that there is significant preferential absorption of 755-nm light by melanin over hemoglobin when compared with 532-nm and 1064-nm laser energy. Table 1 shows the relative melanin and hemoglobin absorption. These data compare the thresholds for LIOB formation in the epidermis with these chromophores at different



FIG. 6 Clinical appearance before and after treatment with the picosecond Alexandrite at 755 nm with the diffractive lens array. (Courtesy of David H. McDaniel, MD, Virginia Beach, VA; with permission.)



FIG. 7 A 755-nm picosecond Alexandrite with the diffractive lens array after 2 treatments. (Courtesy of Raminder Saluja, MD, Huntersville, NC; with permission.)

concentrations of melanin. The authors also correlate these thresholds to blood temperature increase. These findings highlight the preferential absorption of melanin over hemoglobin at 755 nm with an apparent 54:1 ratio, as opposed to the 16:1 ratio at 1064 nm and a 2.4:1 ratio

at 532 nm. This information has practical implications. The wider the separation of absorption of melanin to hemoglobin, the less likely there will be targeting blood in vessels and the lower the probability that there will be superficial hemorrhage.

TABLE 1
Absorption Coefficients for Melanin and Blood for the 3 Laser Wavelengths Used for Calculation of the Laser-Induced Optical Breakdown Threshold Fluence and the Corresponding Temperature Increase in Blood-Filled Capillaries at the Dermal/Epidermal Junction

Wavelength, nm	532			1064			755		
Melanin abs, cm ⁻¹	555			50			163		
Blood abs, cm ⁻¹	235			3.2			3.0		
Absorption ratio	2.4 : 1			16 : 1			54 : 1		
Epid. Melanin %	2%	15%	43%	2%	15%	43%	2%	15%	43%
LIOB Thresh, J/cm ²	2.8	2.7	2.6	31	30	29	9.5	9.1	8.8
Blood Temp rise, °C	172	105	40	28	25	22	7.8	6.5	4.8

SUMMARY

The new generation of picosecond lasers that have been developed for tattoo removal has largely lived up to the expectation that they would provide more rapid clearances of tattoos. The difference is most pronounced when comparing these new lasers with the old 40- to 50-nanosecond QS lasers. The shortened pulse duration has resulted in less thermal damage to the skin and therefore less pain and less peripheral tissue damage. The fractional delivery of this energy has created a localized injury largely confined to the epidermis. Controlled, localized tissue injury results in dermal as well as epidermal rejuvenation and remodeling. This type of nonablative damage is well suited to individuals who are interested in minimal downtime. This treatment is also appropriate in darker skin types that are prone to dyspigmentation with more aggressive procedures. With melanin as the primary target, people of color finally have a treatment whereby epidermal pigment confers a benefit.

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Hair Biology and Androgenetic Alopecia

Diagnosis, Neogenesis, and Management

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KEYWORDS

- Hair follicle • Hair cycle • Stem cell niches • Diagnostic tests • Androgenetic alopecia
- FDA-approved and novel therapy

KEY POINTS

- Hair development, cycling, and androgenetic alopecia are believed to be significantly triggered by molecular and cellular stem cell activity.
- Typical normal hair characteristics define lanugo, vellus, intermediate, and terminal hairs.
- Complete personal, family history, diagnostic tests, and clinical presentations determine the type of alopecia and therapeutic alternatives.
- The precise etiology for the development of male and female pattern baldness, including telogen effluvium, are unknown, which is a challenge for directed therapies.
- A knowledge of medications approved by the Food and Drug Administration (FDA) and novel approaches that can provide safe and effective stand-alone or combined remedies in conjunction with surgical procedures.

INTRODUCTION

Scalp hair normally serves various physiologic roles that include protection against excessive exposure to ultraviolet radiation [1] and cold temperatures, as well as defining an individual's social, sexual, and health well-being [2]. The occurrence of androgenetic alopecia (AGA) in previously vibrant healthy individuals can produce devastating psychological impacts as thinning, shortening, or loss of hair progressively advances. Because male pattern hair loss (MPHL) and female pattern hair loss (FPHL) affect more than 50% of men and nearly 50% of women [3] by 50 years of age, concerned individuals often

seek treatment advice from primary care physicians, dermatologists, or cosmetic surgeons. Physicians must be well-informed to recommend to their patients safe and effective therapies and avoidance of "miracle" cures. Fundamentals for hair loss counseling and management include a sophisticated understanding of the development, regulation, and dysregulation of hair follicles in both normal and diseased conditions.

Previous extensive investigations of hair development in both invertebrates [4] and in mice [5] have added clarity to the morphologic and cyclical transformations. Schofield [6,7] first proposed the term,

Disclosure Statement: The author has nothing to disclose.

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"niches," in hematopoietic tissues to describe slow cycling stem cells in specialized domains. Stem cells within similar domains have also been observed within human hair follicles and were found to leave their niches and evolve into rapidly dividing transit-amplifying to dynamically proliferate and commit to terminal differentiation.

MPHL, FPHL, and telogen effluvium (shedding) are believed to be affected by molecular and cellular disturbances during hair cycle regulation initiated by a variety of triggers; that is, hormones, stresses, drugs, metabolic and nutritional deficiencies, immunologic alterations, and diets. In general, the mechanism of action of these damaging factors is not fully understood or controllable. As investigators continue to identify more putative mediators and attempt to regulate the complex cross-communications within the stem cell hierarchy, new innovative therapeutic approaches may be possible to stimulate more effectively hair growth in MPHL/FPHL conditions, enhance follicular growth after transplantation, and treat other acquired diseased conditions.

The purpose of this article was to provide current information on the biology, potential stem cell-based pathophysiology, diagnostic tests, clinical presentation, Food and Drug Administration (FDA)-approved approaches, and novel non-FDA-approved treatments for patterned hair loss.

HAIR DEVELOPMENT

Hair follicles are organized into many heterogeneous cell types in stem cell habitats that interface with each other in a hierarchical manner during embryonic and postnatal cycling (Fig. 1). In a review by Schmidt-Ulrich and Paus [8], *de novo* initiation of follicle development in mice embryos was contingent on reciprocal cross-talk between single layered primitive epidermal cells (*placodes*) and dermal mesenchymal cells (*condensates*) regulated through canonical Wingless (Wnt) and Hedgehog (Hh) pathways via β -catenin transcription factors, receptors, ligands, and adhesion molecules. The undifferentiated *placode* cells (Stage 1) are transformed into *primary germ center* [9] (Stage 2), composed of a population of quiescent histone label retaining cells (LRCs) with specified stem cell markers, such as Sox9 proteins. As epithelial hair germ cells plunge downward forming the hair peg and the outer root sheath (ORS), a trail of Sox9 LRC cells congregates into another niche, called the bulge (Stage 3–5). These specialized bulge LCR Sox9 stem cells are located subjacent to the ORS and positioned between the sebaceous gland units and opposite to the point of insertion of the arrector pili muscle. Progeny of the LRC Sox9-derived bulge stem cells are a requirement for formation of the sebaceous gland lineage and the later described hair germ, both of which promote cyclic phases of postnatal follicles

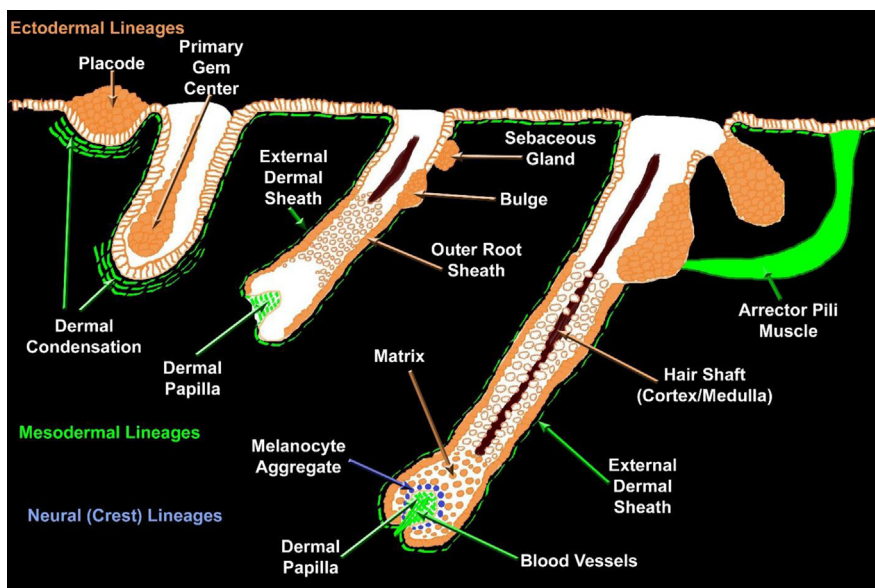


FIG. 1 Schematic representation of hair follicle morphogenesis during nascent development by germ stem cells and their niches from Stage 0 to Stage 8.

in the nude mice model. As the LRC Sox9 stem cells travel downward toward the proximal bulb, a highly proliferative, transit-amplifying Sox9 progeny, called matrix cell [10], gathers just above the bulb, and will play a leading role in the eventual formation of the inner root sheath, cortex, and medulla of the nascent hair (Stages 6–8) via a cascade of signals [11]. In developmental waves [12], melanocytes arrive to populate the central core of the hair shaft and external root sheath, accompanied by migrating hematopoietic cells and neurotrophin-induced nerve cells that form capillary loops and nerve innervations located around the mesenchymal-derived dermal papilla.

As mentioned previously, once epithelial *placodes* have formed in Stage 1, cues from *placode cells* induce the assemblage of mesenchymal *condensate cells* [13], which release their own molecular message of signals and transcriptional factors to facilitate the downward migration of epithelial cells (Stage 2). The mesenchymal stem cells in the dermal *condensates* also begin their own journey downward during Stages 3 to 5, external to the advancing epithelial columns, and eventually form into the *dermal sheath* and proximal

dermal papilla at the base of the nascent follicular bulb. The dermal sheath stem cells have been considered a cellular reservoir for dermal papilla cells and can regenerate a new dermal papilla after its loss. The dermal papilla stem cells participate in epithelial-mesenchymal cross-talk through their unique gene signature molecules with the surrounding epithelial cells of the matrix, ORS to induce *de novo* follicle development during Stages 6 to 8 with cycling and stimulated hair growth [14].

HAIR CYCLING

Normal cycling hair follicles undergo complete loss and regeneration of the inferior nonpermanent portion of the terminal hair and are driven by niche epidermal and dermal stem cells in an asynchronous manner through stages of *anagen* growth phase (2–6 years), transitioning through brief *catagen* shrinking phase (3–4 weeks), and ending in quiescent miniaturized *telogen* phase (3–4 months) (Fig. 2). Recently, an additional phase, called *exogen*, was recognized when the passively retained hair shaft is actively shed from the telogen follicle.

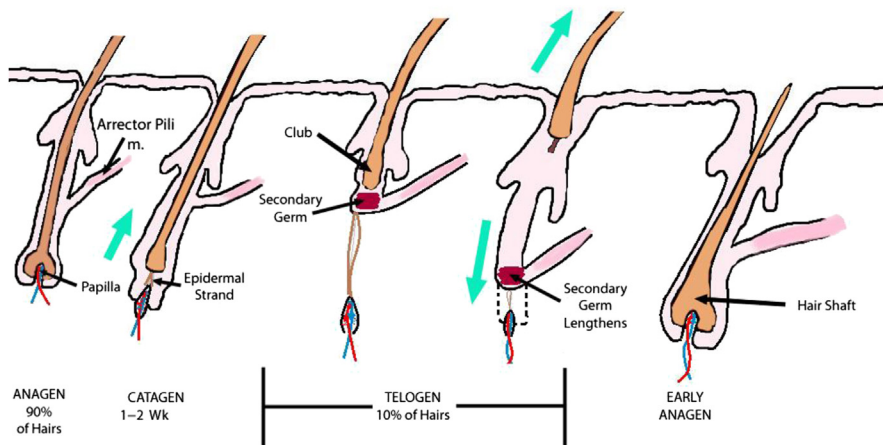


FIG. 2 Schematic representation of normal mature follicle cycling from anagen growth, catagen regression, and telogen resting phases. Legend for DVD. PRP has emerged as a novel new treatment that might have a beneficial role in hair regrowth. It is proposed that the stimulatory growth factors released from the α -granules in platelets may act on the stem cells in the bulge and dermal papillae areas of follicles and promoting neovascularization. The safety and efficiency for its salutary results are increasingly being investigated through investigational research board studies with a larger cohort of subjects who have male and female androgenetic hair loss. Current investigational protocols are under way to evaluate the effects of differing concentrations of PRP, number and intervals of treatment sessions, and the additive benefits of combined usage with fat, cosmeceutical growth factors, and low-level light therapy. This DVD demonstrates one method that is under study to validate the safety and effectiveness of PRP for the treatment of MPHL.

Anagen phase is characterized by actively dividing cells in the bulb above and around the dermal papilla and epidermal-derived matrix to form elements of the hair shaft. Catagen phase is believed to be initiated by apoptotic signals released from exhausted matrix cells that trigger inhibitory transcriptional pathways from the dermal papilla. These inhibitory signaling molecules activate the catagen-telogen hair germ, located above the matrix-bulb, to direct the sequential loss of the lower follicle, leaving a thin epithelial strand, called the fibrous streamer [15]. Telogen phase is marked by a complete interruption between the nonpermanent and permanent portions of the follicle that has retracted to form the club hair demarcated at the level of the bulge and arrector pili attachments. The crenated dermal papilla, releasing inhibitory signaling molecules to suppress bulge and hair germ activities, has translocated itself distally in the lower dermis [16,17]. After a short telogen period, the 3 stem cell niches (hair germ, dermal papilla, and bulge) are believed to coordinate cellular stimulation or inhibition to recapitulate an entire new lower follicle and shaft [18,19]. Toward the end of telogen, regulating molecular mechanisms [16] remain unclear, but most likely involve the bursting of hair germ cellular activity to fuel the initial stages of telogen-anagen regeneration. The bulge niche appears to act more as the engine that maintains progression of the hair cycle and is the reservoir of long-term stem cells.

STEM CELL DYSFUNCTION IN ALOPECIA

Elegant studies [20–23] from global gene expression patterns, unique cell-surface marker CD200, intermediate filament protein KRT15, and transcriptional profiles of Wnt inhibitors WIF1 and DKK3, have suggested that overrepresented keratinocyte stem cells, isolated from bulge niches in human scalp anagen follicles, represented the progeny of the slow cycling ORS-LRCs. In

human bulge-ORS cells, CD34 expression was low or absent but was most highly expressed and confined to cells in the sub-bulge region of the ORS of the anagen hair follicle. These cells underwent apoptosis at the end of anagen and were considered to be a bulge-derived progenitor population [24].

Garza and his group [25] reported that KRT15, ITGA6, and CD200 expressions in stem cell bulge populations in AGA anagen bald and hair (nonbald) scalp were maintained at normal levels, but CD34 progenitor cells in the sub-bulge region were significantly diminished. Because the hair germ cells and matrix cells arose from bulge and sub-bulge cells at the end of catagen and were believed to be immediately responsible for the formation of the new lower hair follicle at anagen, any loss of progenitor cells in the sub-bulge region might lead to miniaturized or loss of anagen follicles and eventually baldness. Other investigators [26] similarly postulated that miniaturization in AGA might result from diminished conversion of hair follicle bulge stem cells to progenitor cells. Further investigations are needed to determine whether the loss of these cells represents a primary or secondary event in AGA.

NORMAL HAIR DEMOGRAPHICS

The total number of anagen scalp hair follicles in an adult is estimated between 100,000 and 250,000, but the number varies depending on the individual's ethnicity, hair color, age, and sex. Because the average scalp area is approximately 500 cm², the calculated normal density averages approximately 200 hairs/cm². The typical growth rate of anagen hair averages between 0.3 and 0.3 mm/d, whereas the typical shed rate averages 50 to 100 hairs per day. In clinical practice, a distinction is made among lanugo, vellus, and intermediate and terminal hairs, based on differences in their shaft diameters, lengths, pigmentations, and depths (Table 1).

TABLE 1
Typical Hair Characteristics

Type	Shaft Diameter	Medullated/Pigmentation	Length	Depth
Lanugo	<30 μ m	Nonmedullated/poorly pigmented	<0.5 cm	Upper dermis
Vellus	<30 μ m	Nonmedullated/poorly pigmented	<2.0 cm	Upper-mid dermis
Intermediate	30–50 μ m	Medullated/pigmented	>2.0 cm	Mid-deep dermis
Terminal	>50–100 μ m	Medullated/pigmented	>2.0 cm	Deep dermis/subcutaneous fat

DIAGNOSTIC TEST FOR ANDROGENETIC ALOPECIA

For the diagnosis of AGA, a complete personal (medications, treatments, concomitant diseases) and family history are required to guide the clinical examination. A description of hair loss, age of onset, acute or chronic duration, focal or diffuse distribution, associated symptoms, and the evolutionary course are important to diagnose AGA or *telogen effluvium*. More laboratory tests might be necessary to confirm findings in individual cases. In women, a first-line blood test, such as a complete blood count, erythrocyte sedimentation rate, serum ferritin, thyroid profile, and complete hormonal panel is recommended. In men, it might not be necessary to obtain first-line blood test for MPHL, unless diffuse FPHL is suspected.

Several clinical tests might be carried out when faced with a diagnostic dilemma. A Pull Test, performed by grasping 50 to 70 hairs, might be useful in delineating active areas of alopecia. In male or female AGA, for example, the removal of more than 6 hairs in the frontal-crown scalp indicates a “positive” Pull Test, whereas a “negative” Pull Test is usually 0 to 3 hairs in the occiput. If positive diffusely, including the occipital scalp, a diagnosis of telogen effluvium should be considered. Other more sophisticated tests, such as phototrichography, dermatoscopy, and dynamic growth rates after shaving procedures, might provide additional diagnostic information for improved treatment plans.

ANDROGENETIC ALOPECIA

AGA represents a general term for hair loss that typically acquires the characteristic MPHL or FPHL. In MPHL, AGA is mediated principally by the conversion of testosterone to dihydrotestosterone by the enzyme *5 α -reductase type II* and presence of androgen receptors in the dermal papilla in genetically susceptible hair follicles [27]. In FPHL, the evidence for an androgen-dependent trait is present in some cases, but other nonandrogenic environmental pathways may play more prominent roles. Although MPHL and FPHL share common histopathological findings but different clinical presentations, current genome-wide association studies suggest their etiologies may not necessarily be the same [28].

MALE PATTERN HAIR LOSS AND TREATMENT

MPHL is believed to be due to a polygenic mode of inheritance [29] and is characterized by its typical bitemporal recession, balding to the vertex and crown areas,

and occipital sparing, as defined in Hamilton-Norwood's classification [30], whereas diffuse thinning with an intact frontal hairline is referred to as an FPHL variant in men. A common pathway of follicular miniaturization occurs with progressive reduction of anagen duration, prolongation of telogen, and minimal inflammatory fibrosis with associated clinical findings of a mixture of terminal, intermediate, and vellus-sized hairs and a negative Pull Test in long-standing AGA.

Hair transplantation or surgical reduction procedures, and hairpieces are viable options for some male patients. Both the FDA [31] and a European consensus group [32] recommended only finasteride, a competitive inhibitor of type II *5 α -reductase* enzyme, and topical minoxidil, a potassium channel opener and vasodilator, for MPHL based on sufficient evidence base medicine data. Recent articles have summarized each of their bio-pharmacological actions [3,33] and adverse events [3,34].

FEMALE PATTERN HAIR LOSS AND TREATMENT

FPHL remains a poorly understood complex, especially about the roles that genetic factors, inflammation, or hormonal or vascular influences play [35]. Although androgen dependency is generally the most common form of hair loss in men, the involvement of androgens in patterned or nonpatterned hair thinning or loss has not been as well established in women [36]. FPHL often can be precipitated and exacerbated by drugs, acute stress, diet, hormonal changes, weight loss, and partum [37]. FPHL, described as regressive or senescent alopecia, is characterized by progressive shortening of the anagen phase, a lengthening of the latency period, and miniaturization into villus-like hair [38]. Such changes lead to diffuse loss of hair density, affecting primarily the midline vertex and centro-frontal scalp, defined by different grading systems [33]. Minoxidil dose-dependent placebo-controlled studies [39] determined that the FDA-approved marketing of topical 2% or 5% concentrated solutions was safe and effective for temporary AGA improvement in men and women and for post-hair transplantation [40,41], appearing to prolong the duration of anagen, reverse miniaturization, and reduce postsurgical telogen effluvium.

TELOGEN EFFLUVIUM AND TREATMENT

Telogen effluvium (TE) is believed to occur in apparently healthy women and is attributed to an

asynchronization disorder whereby generalized hair shedding (teloptosis) of greater than 20% existed than observed in MPHL or FPHL [42]. TE can start 2 weeks after a trigger but peaks between 6 and 8 weeks and then improves approximately 2 months after the trigger is removed or treated. Bouhanna and Bouhanna [43] clearly summarized etiologic triggers, diagnostic tests, and treatment prognoses in acute and chronic (longer than 6 months duration) cases.

NOVEL APPROACHES TO ANDROGENETIC ALOPECIA

Regenerative medicine, in which the patient's own platelet-rich plasma (PRP), stem cells, adipose tissue, growth factors, conditioned media, and low-level light therapy has now become viable alternatives to conventional therapies. Although the FDA has approved these medical devices through a 510K regulation, the status simply demonstrates safety rather than efficacy. As yet, there are no approved indications or pathways for their usage in alopecia.

PLATELET-RICH PLASMA

Platelets release more than 20 types of growth factors that include platelet-derived growth factor, fibroblast growth factor, hepatocyte growth factor (HGF), transforming growth factor, vascular endothelial growth factor, epithelial growth factor, and insulin-like growth factor. Growth factors are believed to be generally responsible for angiogenesis [44], stem cell proliferation and differentiation [45], and antiapoptotic properties [46], but specifically for hair follicles, anagen induction [47], cyclic growth [48], follicle development [49], and proliferation of dermal papilla cells [50].

There are several recent clinical studies [51–54] suggesting a benefit of PRP for the treatment of AGA. A video of PRP and low-level light therapy treatment accompanies this article.

ADIPOSE TISSUE AND STROMAL VASCULAR FRACTION

Recent reports [55,56] suggest that adipose tissue is an integral part of the normal hair cycle, and that its reduction parallels hair loss and prolongation of the telogen phase. A recent pilot study [57] suggests that scalp stromal vascular fraction-enriched fat grafting may represent a promising approach for AGA.

CONDITIONED MEDIA

The use of secretory factors in cluster differentiation (CD) from adipose-derived stem cell cultures for hair loss has advantages of transportable packaging and the absence of tissue matching between donor and recipient [58]. A few clinical trials [59] have suggested a promising strategy for AGA with no significant side effects.

LOW-LEVEL LIGHT THERAPY

Several devices on the market have reported to improve AGA by using multicentered, sham-controlled, double-blind approaches [60–62]. Further studies will be required to confirm its role in the treatment of hair loss.

SUMMARY

Although practitioners in their clinical practice strive to practice evidence-based medicine, the successful management of MPHL, FPHL, and TE is based on astute judgment and experience. Strategic planning varies according to the clinical stage of AGA and responses to approved medico-surgical treatment options. Fundamental to the Good Practice of Medicine for alopecia consist of a profound understanding of follicular biology, stem cell functions and dysfunctions, incorporation of useful tests, and a flexible approach to approved options. Practitioners should be open to novel treatments that possess significant therapeutic potentials from on-going trials under the auspices of the FDA.

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Platelet-Rich Plasma

Fact or Fantasy?

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KEYWORDS

- Platelet-rich plasma • PRP • Platelet-rich fibrin • Growth factors • Autologous platelets
- Autologous injectables

KEY POINTS

- Platelet-rich plasma (PRP) is an autologous solution drawn from one's blood that has been centrifuged and filtered to contain a high concentration of platelets and their bioactive growth factors.
- PRP has been applied in numerous ways in multiple medical and surgical fields, particularly in cosmetic medicine and surgery because of its potential rejuvenating effects.
- In cosmetic medicine and surgery, PRP has been described to improve wound healing, reduce hypertrophic scars, enhance fat grafting, promote hair growth, rejuvenate the skin, and serve as an adjunct for other cosmetic procedures, but the evidence in support of the true efficacy of PRP is limited.
- The reported PRP isolation protocols vary significantly, and until an optimal and standardized isolation protocol is agreed on, it will be difficult to appropriately evaluate the efficacy of PRP in cosmetic medicine and surgery.

INTRODUCTION

Platelet-rich plasma (PRP) is an autologous solution of highly concentrated platelets and their associated bioactive factors. The use of PRP has become a controversial topic in medicine since its introduction in the 1970s. Multiple fields, including orthopedics, rheumatology, cardiology, gynecology, ophthalmology, physical medicine and rehabilitation, and oral maxillo-facial surgery, have sought to understand the mechanism of PRP activity, optimize its efficacy, and apply it in different clinical scenarios. Because PRP contains growth factors that are integral to inflammatory processes and wound healing, its application is also of significant interest in cosmetic plastic surgery and dermatology.

During the past 2 decades, multiple studies, case series, and case reports have been published describing the potential applications of PRP in cosmetic surgery and medicine. Physicians are searching to determine how PRP may be applied in minimally invasive rejuvenation, making PRP a popular topic at national and international cosmetic conferences. As with many products and procedures in cosmetic surgery, PRP has found its way into popular media, and celebrities are now advocating for procedures like the "Vampire Lift and Vampire Facial." As such, increasingly more patients are now coming to physicians requesting PRP-based therapies.

Although the attention surrounding PRP is intriguing, it is important for physicians and other practitioners to step back and critically evaluate the evidence on the

Disclosure Statement: I. Percec serves as a consultant for Galderma. The other authors have nothing to disclose.

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effectiveness of PRP therapies. Because PRP is being touted as having numerous applications in cosmetic surgery, it is the duty of the treating physician to understand the data, on both a basic science level and a clinical level, for each proposed indication, before use of PRP in patient care.

This article informs the reader on the following: (1) the history of PRP; (2) the current definition of PRP and its functional components; (3) how PRP is currently isolated and classified; (4) current PRP applications in the field of cosmetic surgery and the scientific evidence on these indications; (5) potential adverse effects; and (6) the future of PRP therapies.

THE HISTORY OF PLATELET-RICH PLASMA

It is difficult to set a date on the exact origin of PRP given that there are so many forms of “platelet-rich plasma” formulations. In 1970, Matras described the allogeneic fibrin glue formed by polymerizing fibrinogen with thrombin and calcium [1]. In 1990, Gible and Ness described an autologous fibrin gel with hemostatic properties [2]. In 1998, Marx and colleagues [3] first described PRP’s potential regenerative properties when they described its ability to enhance bone grafts in oral surgery. Eventually, the more modern conception of PRP was described, which shifted the focus away from recombinant growth factors. The allure of an autologous source of platelets containing active growth factors was, in part, because of the avoidance of recombinant growth factors that were limited by high cost, suboptimal delivery to target tissues and cells, and short half-lives. As a result, over the past 2 decades, the use of autologous PRP, without exogenous factors, has grown in many medical and surgical specialties.

DEFINITION AND FUNCTIONAL COMPONENTS OF PLATELET-RICH PLASMA

PRP is an autologous solution isolated from one’s blood that has been centrifuged and filtered to contain a high concentration of platelets, often 3 to 4 times higher than physiologic concentrations [4]. The functional component of PRP is the platelet (thrombocyte), a membrane-bound cellular fragment, and the bioactive molecules stored in its alpha and dense granules. The principle behind the medical application of PRP is the ability to deliver high concentrations of activated physiologic growth factors to specific cells and tissues. Although there are more than 30 bioactive molecules contained in platelets, the most important ones are cell adhesion molecules, namely, fibrin, fibronectin, and vitronectin, that aid in

hemostasis, as well as 7 key growth factors: connective tissue growth factor, epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor [4]. Each of these growth factors has specific functions, but all play a role in inflammation and wound healing (Table 1).

TABLE 1
The 7 Most Important Growth Factors in Platelet-rich Plasma and Their Physiologic Effects

Growth Factor	Physiologic Effect
Connective tissue growth factor	Promotes fibrosis Stimulates white blood cell and platelet adhesion, migration, and proliferation Promotes angiogenesis
EGF	Activates keratinocytes Promotes reepithelialization Maintains skin integrity Stimulates epithelial, mesenchymal, and endothelial mitogenesis
FGF	Promotes endothelial proliferation and organization Promotes angiogenesis Mitogenic Promotes proliferation of fibroblasts Stimulates epithelial proliferation, migration, and differentiation Regulates tissue remodeling
IGF	Regulates epithelial growth and development
PDGF	Promotes fibroblast, smooth muscle, and glial mitogenesis Regulates tissue remodeling Regulates cellular differentiation Promotes angiogenesis Regulates cellular division of fibroblasts Maintains proliferation of oligodendrocyte progenitor cells
TGF	Promotes synthesis of extracellular matrix Stimulates fibroblast and keratinocyte proliferation Promotes angiogenesis
Vascular endothelial growth factor	Promotes angiogenesis Promotes lymphangiogenesis

Under physiologic conditions, platelets store the bioactive factors in granules. During clotting, platelets adhere to exposed collagen and von Willebrand factor from damaged endothelial cells. They are then activated by thrombin, thromboxane A2, adenosine 5'-diphosphate, collagen, or platelet-activating factor and undergo degranulation to release their stored products [5]. When activation occurs, platelets release approximately 95% of their stored growth factors immediately [6]. Most of these growth factors have half-lives on the order of hours, and platelets themselves only have a lifespan of about 10 days [7–9].

It is important to understand normal platelet physiology when thinking about how PRP works, because this will have a significant effect on PRP isolation and administration, relative to treatment timing and frequency. For instance, to prevent premature aggregation of the platelets before administration, many providers add an anticoagulant to PRP. Then, to displace the anticoagulant and stimulate degranulation upon administration of PRP, an activating agent may be added. Of note, when using PRP in surgical sites, one does not need to use an activating agent because the platelets will be activated physiologically by being exposed to collagen.

Consequently, the functionality of PRP depends in large part on how it is isolated. The concentration of viable, undamaged, platelets directly affects the amount of available growth factors. The efficacy of PRP has been demonstrated to follow a dose-response curve, although, in general, a concentration of 1×10^6 platelets per milliliter has been determined to be physiologically active [4,10,11]. The use of an anticoagulant and/or an activating agent also affects the kinetics of growth factor activity [5]. Furthermore, the concentration of leukocytes, which may or may not be included in the final PRP solution, also alters PRP's function [5]. Finally, it is important to consider what medications the patient is taking, because many medications, such as aspirin, impact platelet function [5]. Understanding that many of the steps in isolating PRP affect the final product and its function is essential when reviewing the literature, because each study presents the results of its own formulation of "platelet-rich plasma."

ISOLATION OF PLATELET-RICH PLASMA AND CLASSIFICATION

PRP is prepared in a sequential manner with multiple steps during which the practitioner can specify the settings and thus alter the final product (Fig. 1). First, whole blood is collected from the patient via standard venipuncture and centrifuged to separate it into 3 layers:

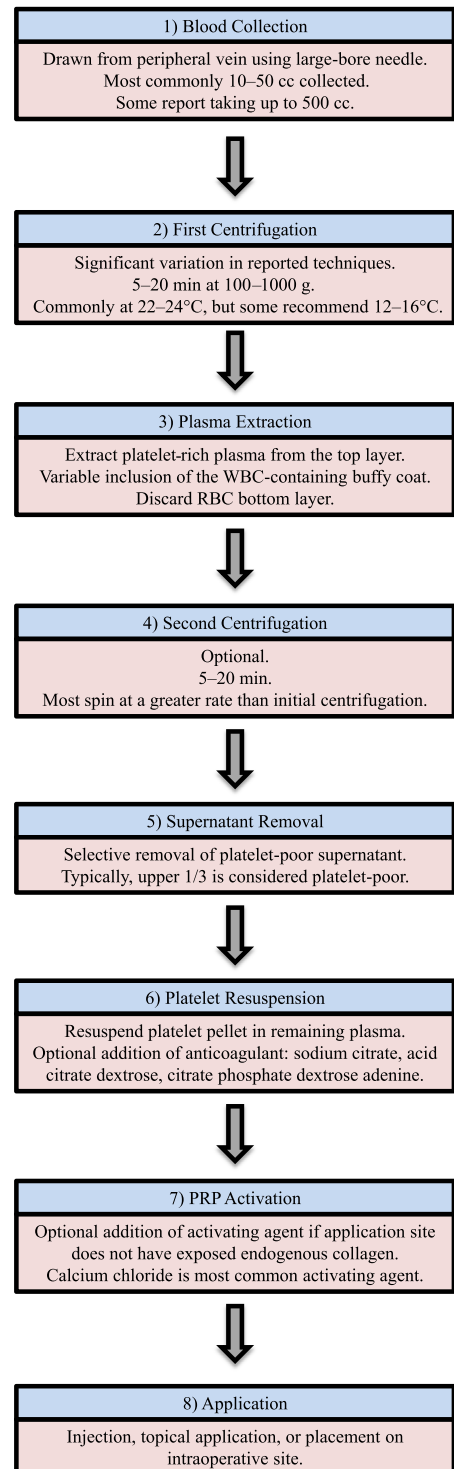


FIG. 1 PRP isolation protocol and commonly reported parameters. RBC, red blood cells; WBC, white blood cells.

the highly dense erythrocyte layer at the bottom, the protein-rich plasma on the top, and the buffy coat in the middle, which includes the leukocytes. The plasma and buffy coat solution may be centrifuged for a second time to selectively remove the platelet-poor supernatant. The platelet-enriched solution may have an anticoagulant added, such as sodium citrate, acid citrate dextrose, or citrate phosphate dextrose adenine, to prevent premature platelet aggregation before administration. Finally, before administration, an activating agent, such as calcium chloride, may be added to stimulate platelet degranulation upon administration.

Each one of these steps can be tailored for a specific PRP application by practitioners. For example, one can choose the time and force of the initial centrifugation and whether to repeat the centrifugation step on the platelet and buffy coat solution. These variables can significantly affect platelet viability in addition to concentration enrichment. The user also determines how much of the buffy coat layer is aspirated to alter the leukocyte concentration. Finally, the user can determine whether to activate the platelet solution and what activating agent to use, and whether to use an anticoagulant and what anticoagulant to use. Multiple studies have confirmed significant differences in platelet, growth factor, and leukocyte concentrations when isolating PRP according to different protocols [12–26].

Because of the significant variability in the isolation of the platelet-rich solution, several groups have proposed classification schemes in an attempt to standardize PRP preparation. Dohan Ehrenfest and colleagues [27] classified the solutions into 4 categories according to the presence of leukocytes and the formation of a fibrin matrix from anticoagulant use: (1) pure platelet-rich plasma (P-PRP), (2) leukocyte-rich platelet rich plasma (L-PRP), (3) pure platelet-rich fibrin (P-PRF), and (4) leukocyte platelet-rich fibrin (L-PRF). Although P-PRP and L-PRP are liquid platelet suspensions, P-PRF and L-PRF are fibrin-based gels [27]. Although this initial classification has been used by many studies to describe the PRP solution being used, Frautschi and colleagues [5] recently presented their own expanded classification system, the FIT PAAW. The FIT PAAW classification is based on the steps and factors that can be modified during the PRP preparation process and therefore affect the functionality of the final product: (1) Force of centrifugation, (2) Iteration or sequence of centrifugation, (3) Time of centrifugation, (4) Platelet concentration, (5) Anticoagulant use, (6) Activator use including type and amount, (7) White blood cell composition [5]. This classification addresses all currently modifiable steps in PRP production.

Irrespective of this, it is critical for clinicians and investigators to clearly specify the exact protocol used in a given publication or presentation.

CURRENT PLATELET-RICH PLASMA APPLICATIONS

Does Platelet-rich Plasma Improve Wound Healing?

Although not the focus of this review, PRP has been applied and studied most extensively for wound healing. Multiple groups have reported success with using PRP to treat burn wounds, improve skin graft take, and to heal diabetic ulcers, venous stasis ulcers, and traumatic wounds [28–30]. It has been proposed that the growth factors released by platelets stimulate fibroblasts and inflammatory cells to promote healing and collagen and ECM protein production, keratinocytes to increase epithelialization, endothelial cells to undergo neovascularization, and signal through other mechanisms to facilitate nutrient delivery and overall wound healing [28–30]. Despite numerous groups touting these significant benefits, the 2016 *Cochrane Review* concluded that the overall quality of evidence in favor of PRP promoting wound healing is low, given the lack of blinded, randomized, placebo-controlled trials and the potential for publication bias. Despite this, many groups rely on anecdotal data and continue to use PRP in their practice for wound healing [31].

Does Platelet-rich Plasma Improve Scar Appearance?

Because of the connection between wound healing and scar formation, it was proposed that PRP may help reduce the appearance of scars through the effect of its growth factors on fibroblasts and collagen remodeling. Unfortunately, the techniques described for using PRP to reduce the appearance of scars are highly varied, thus making it difficult to make any definitive conclusions regarding its effectiveness in this application.

Most studies on the subject have described using PRP as an adjunct to fractional laser resurfacing of scars. Lee and colleagues [32] performed a split-face trial on 14 patients with acne scars receiving ablative CO₂ fractional resurfacing and found that the PRP-injected side had shorter durations of edema, erythema, and crusting compared with the saline side. Tenna and colleagues [33], Zhu and colleagues [34], Gawdat and colleagues [35], and Abdel Aal and colleagues [36] similarly reported a synergistic effect of PRP on laser skin resurfacing healing. In contrast, Faghihi and colleagues [37] performed a split-face trial on 16 patients receiving

ablative fractional CO₂ laser and found no difference in clinical improvement between PRP and saline injections, but the PRP group had increased erythema and edema.

The other common technique to improve scar appearance combines PRP and microneedling. Ibrahim and colleagues [38] randomized 90 patients with atrophic acne scars to microneedling, PRP injections, or alternating microneedling and PRP injections. Unblinded photographic analysis revealed significant improvement pretreatment to posttreatment for all groups, with the combination therapy being superior [38]. Asif and colleagues [39] performed a split-face trial on 50 patients with acne scars receiving microneedling and found that the side treated with topical and injected PRP had greater clinical improvement than the side injected with distilled water. Chawla [40] found that microneedling with PRP was superior to microneedling with vitamin C. In contrast, Kotb and Ibrahim [41] found no added benefit of topical PRP to microneedling in the management of atrophic acne scars.

A variety of other PRP-combination techniques have been tested to optimize scar appearance. Nofal and colleagues [42] randomized 45 patients with acne scars to PRP injections, trichloroacetic acid peel, or microneedling with PRP. They found that all groups had significant improvement in scar appearance relative to baseline but no difference among treatment groups [42]. Gentile and colleagues [43] found that PRP-enriched fat grafting improved the appearance of facial scars. Furthermore, Cervelli and colleagues [44] and Nita and colleagues [45] found that PRP with fat grafts combined with laser resurfacing improved the appearance of scars.

It remains to be determined if PRP, either alone or in conjunction with lasers, microneedling, chemical peels, fat grafting, or other adjunct modalities, does improve the appearance of scars. Unfortunately to date, no randomized, blinded, placebo-controlled studies have been performed, and the evaluation of most of the prospective studies and split-face studies has been subjective. Furthermore, most investigations describe combination treatments, or have differing treatment comparisons, making determining the effect of PRP itself on scar appearance challenging.

Does Platelet-rich Plasma Enhance Fat Grafting?

Fat grafting has many applications in cosmetic surgery, most frequently as an inexpensive, long-lasting, autologous soft tissue volumizing application. Although the

number of fat grafting procedures and its indications has continued to increase, this technique does suffer from limitations. Fat graft viability and degree of fat necrosis vary significantly, depending on the individual patient, fat preparation, the donor site, and the recipient site, among other parameters. Unfortunately, one cannot predict the outcomes of fat grafting in a given patient, which may result in contour irregularities from differential fat graft take and later development of oil cysts and fat necrosis calcifications. As a result, many groups are working to determine how to increase fat graft survival by making fat grafting more reliable and predictable.

Fat grafts initially survive through nutrient diffusion from the plasma, and then, about 48 hours after transplantation, neovascularization begins, which enables long-term graft survival [46–50]. In addition, with neovascularization, multipotent adipose-derived stem cells (ADSCs) proliferate to maintain the stem cell pool and differentiate into mature adipocytes to promote graft survival [46]. PRP, with its abundant supply of growth factors, was hypothesized to increase fat graft survival by (1) facilitating nutrient support from its plasma component, (2) promoting angiogenesis, and (3) stimulating the proliferation and differentiation of ADSCs [51]. Multiple preclinical and clinical studies have been conducted to examine the effect of PRP on fat grafting.

Unfortunately, a blinded, placebo-controlled, randomized trial has yet to be performed to examine the effect of PRP on fat grafting in humans. The preponderance of the data regarding the clinical efficacy of PRP-enriched fat grafting comes from retrospective or prospective case studies, primarily featuring patients receiving fat grafting to the face or breasts. A group from the University of Vergata led by Dr Gentile has conducted multiple studies evaluating PRP-enriched fat grafts [52]. Their study of 13 patients treated with PRP-enriched fat grafts demonstrated 69% graft maintenance by volume at 1 year, which was significantly greater than the 39% maintenance of the 10 patients treated with fat grafts alone [53]. This group conducted a larger study of 100 patients and similarly found a 69% to 39% advantage of the PRP group in fat volume maintenance at 1 year [54]. Gentile and colleagues [55] further reviewed outcomes of 223 patients receiving PRP-enriched fat grafting for either age-related facial volume loss, hemifacial atrophy secondary to Romberg syndrome, or chronic venous lower extremity ulcers. They reported increased fat graft volume maintenance and ADSC proliferation [55]. Finally, the same group conducted an imaging study and found that, 12 months after PRP-enriched fat grafting of the breast, the average resorption rate was

28.2%, oil cyst rate was 45.8%, and microcalcification rate was 20.8%, but there was no control group in this investigation [56]. Other case series similarly reported benefits of PRP in fat grafting [57–59]. One important study to highlight was conducted by Keyhan and colleagues [60] in which they treated half the face of 25 patients with PRP-enriched fat grafts and the other half with PRF-enriched fat grafts. They found that the PRF side had decreased resorption compared with the PRP side, highlighting the fact that different preparations of PRP may have different effects [60]. Although those studies identified a benefit of PRP-enriched fat grafting, Salgarello and colleagues [61] found no benefit of PRP-enriched fat grafting on clinical outcomes, degree of liponecrosis, or need for repeat fat grafting in 17 patients receiving fat grafts to the breast.

The evidence from randomized animal studies on the effects of PRP on fat grafting is more robust. Nakamura and colleagues [62] randomized 64 rats to either conventional fat grafting or PRP-enriched fat grafting and found that the PRP group benefited from increased normal adipocytes and capillary formation and decreased fat resorption. Pires Fraga and colleagues [63] randomized 30 rabbits to either conventional fat grafting or PRP-enriched fat grafting and found that the PRP group benefited from greater fat weight retention and number of viable adipocytes, in combination with fewer areas of necrosis and fibrosis. Rodríguez-Flores and colleagues [64] and Oh and colleagues [65] also reported similar benefits of PRP in their randomized trials. Recognizing the key role of ADSCs in long-term fat graft survival, groups have also looked at the interaction between ADSCs, PRP, and fat grafting. Seyhan and colleagues [66] randomized 40 rats into 4 groups: conventional fat grafting, PRP-enriched, ADSC-enriched, and PRP and ADSC combined enriched fat grafting. They found that the PRP and ADSC combination group experienced the greatest increase in fat graft weight and volume, number of viable adipocytes and blood vessels, and levels of growth factors [66]. Li and colleagues [67] used a mouse model to study the effect of fat grafts supplemented with ADSCs and a varying concentration of PRP. They found that fat grafts enriched with PRP were associated with dose-dependent increases in fat graft take, capillary formation, and ADSC proliferation and differentiation [67]. One important study to highlight was conducted by Zhou and colleagues [68] in which they attempted to create a construct that enables prolonged, sustained release of PRP growth factors as opposed to the immediate release seen when PRP is administered by itself. They used polydopamine to fix the PRP onto gelatin

microspheres, and in their mouse model, found that fat injections supplemented by PRP in this form was associated with more sustained release of growth factors, greater ADSC cell viability, increased fat graft survival, increased neovascularization, and increased CD34⁺ and CD31⁺ cells [68]. In contrast to those positive outcome studies, Por and colleagues [69], in their randomized study of 24 mice, found no difference between the PRP-enriched fat grafts and saline placebo fat grafts in terms of fat graft weight or volume retention.

Several of the preclinical and clinical studies attempted to elucidate components of the mechanism of how PRP may promote fat graft survival. Most groups think PRP may promote fat graft survival through 2 mechanisms: (1) increased neovascularization to promote nutrient delivery and (2) enhancing the function of ADSCs to promote long-term fat viability. However, significant discrepancies have been reported regarding how PRP affects ADSCs by either increased proliferation, differentiation, or both. The University of Vergata group hypothesized that PRP increases ADSC proliferation through upregulation of EGFR and ErbB2 and may work in conjunction with insulin to potentiate the adipogenic differentiation of ADSCs through an FGFR-1 and ErbB2-regulated Akt mechanism [53,70]. Li and colleagues [67] similarly thought that PRP promotes ADSC proliferation because of its mitogenic factors for human mesenchymal progenitor cells. Gersch and colleagues [71] similarly found that PRP augments ADSC growth and proliferation. In contrast to the University of Vergata group, Liao and colleagues [72], Chignon-Sicard and colleagues [73], and Amable and colleagues [74] found that PRP inhibited adipogenesis of ADSCs, hypothesizing that ADSCs cannot proliferate and differentiate simultaneously. Liao and colleagues [72] describe a mechanism for PRP in which PRP favors proliferation as opposed to differentiation by downregulating BMPRIA and FGFR1, which decrease the expression of the adipogenic genes PPAR-gamma and FABP4 in ADSCs. They argue that when PRP is mixed with fat grafts, the released growth factors stimulate proliferation of ADSCs during the acute ischemic period, and then, the ADSCs participate in hormone production and differentiation into adipocytes or endothelial cells after the PRP is resorbed [72]. In contrast, Chignon-Sicard and colleagues [73] hypothesized a TGF- β mechanism for PRP-induced inhibition of ADSC differentiation.

Overall, the evidence in favor of the benefits of PRP on fat grafting is limited, although the data are more positive for PRP having a beneficial effect in fat

grafting than in other PRP-based applications. Although some reviews provide a summary conclusion that favors the use of PRP-enriched fat grafts, all reviews have pointed to the current lack of high-quality, robust evidence [51,75–77]. The clinical evidence is difficult to interpret given the lack of randomized controlled trials and the high variability in techniques. Each study reports its own technique of fat graft preparation, PRP preparation, and how the PRP and fat graft are integrated. The preclinical evidence is a little more robust given that randomized trials have been performed in animal models. However, these studies also vary significantly regarding technique. Some studies isolated fat and PRP from the animals, whereas others isolated them from humans. A limitation of both human and animal studies that applies in particular to the use of PRP in fat grafting is reporting of the PRP concentration. Most report the concentration of PRP by volume in comparison to the fat graft volume, but it is important to remember that equal volumes of PRP taken from 2 different individuals can have greatly different concentrations of platelets and growth factors. Furthermore, few studies report how much of the buffy coat layer is taken, which is important, as Keyhan and colleagues [60] reported significant differences depending on the PRP classification. Finally, although some groups have described the potential mechanism for how PRP promotes fat graft survival, studies do not agree on whether PRP favors ADSC proliferation, differentiation, or both. The results from the clinical and preclinical studies certainly are promising, but much more rigorous studies with consistent and reproducible reporting of techniques are essential before a definitive conclusion can be made about the effect of PRP on fat grafting.

Does Platelet-rich Plasma Promote Hair Growth?

Alopecia, or hair loss, is a common condition that affects men and women of all ages and has a variety of causes. Unfortunately, the most effective medications for hair loss, minoxidil and finasteride, are limited in effectiveness and are better at preventing further loss as opposed to stimulating new hair growth [78]. The hair follicle lifecycle, from proliferation (anagen) to involution (catagen) to resting (telogen), has been demonstrated to be governed by various growth factors. Specifically, EGF, TGF- α , PDGF, FGF, IGF-1, hepatocyte growth factor, keratinocyte growth factor, and nerve growth factor have all been identified as acting on stem cells in the follicle bulge area or on the surrounding dermal papillae to stimulate new follicle

growth and neovascularization [79–86]. Because many of these growth factors are present in PRP, PRP has been widely trialed to treat alopecia by stimulating hair growth.

The first reported application of PRP in hair restoration was in 2006 by Uebel and colleagues [87]. This group performed a split-scalp study on 20 male patients to study the effect of PRP on hair micrograft surgery and found that PRP-treated hair follicular units had a 15.1% greater yield in follicular unit density, relative to the untreated hair follicular units [87]. Following this study, multiple other groups have reported their experience with using PRP to treat alopecia.

The most common cause of alopecia in men and women is androgenetic alopecia (AGA), or pattern hair loss, and multiple studies have tested the efficacy of PRP in treating AGA. Alves and Grimalt [88] conducted a randomized, double-blind, split-scalp study on 12 men and 13 women with AGA in which one side of the scalp was injected with PRP and the other was injected with saline placebo. The side of the scalp treated with PRP benefited from significant increases in hair volume and density relative to baseline and significantly greater hair density relative to the placebo side at 6 months [88]. Similarly, Gentile and colleagues [89] performed a blinded study in which 23 men with AGA had some areas of hair loss injected with PRP and others injected with placebo. Phototrichogram analysis revealed significant increases in hair density and count compared with placebo at 3 months [89]. Furthermore, histologic analysis revealed increases in epidermal thickness, number of follicles, number of Ki67⁺ basal keratinocytes in the epidermis and hair follicular bulge, and small blood vessels around the hair follicles [89]. Additional case series and nonblinded case trials have similarly found a positive effect of PRP on hair growth [90–93].

PRP has also been studied specifically in women with AGA. Tawfik and Osman [94] conducted a randomized, double-blind study comparing intralesional injections of PRP and normal saline placebo in 30 female patients. At 6 months, 83% of had a negative pull test with an average of 3 hairs, compared with 100% having a positive pull test with an average of 10 hairs at baseline [94]. Furthermore, folliscope analysis revealed significant increases in hair density and thickness in PRP-treated regions compared with baseline and to regions treated with normal saline placebo [94]. However, a study conducted by Puig and colleagues [95] failed to identify a significant difference between PRP and saline injections on hair count or mass.

Several studies have looked at combination treatments designed to increase the efficacy of PRP in treating AGA. Takikawa and colleagues [96] combined PRP with dalteparin and protamine microparticles, which facilitate the release of PRP growth factors, and found increased hair count and thickness with histologic findings of thickened epithelium, collagen proliferation, and hair follicle neovascularization, relative to saline control. Kang and colleagues [97], knowing CD34⁺ cells have angiogenic potential, treated patients with a CD34⁺ cell-containing PRP preparation and found that they had greater hair thickness and overall clinical improvement, relative to placental extract control.

PRP has also been demonstrated to be an effective treatment of alopecia areata, an autoimmune cause of hair loss. Trink and colleagues [98] conducted a randomized, double-blind, split-scalp study comparing intralesional injections of PRP, triamcinolone acetate, and placebo for the treatment of alopecia areata in 45 patients. They found that 60% of patients treated with PRP had complete remission with 31% experiencing a relapse, both significantly better than those treated with triamcinolone [98]. Dermoscopic analysis revealed decreased number of dystrophic hairs and increased levels of Ki67, a marker for cellular proliferation [98]. A study by El Taieb and colleagues [99] randomized 90 patients to PRP injections, topical minoxidil, or topical panthenol cream as a placebo. Trichoscopic evaluation revealed PRP had significantly greater hair growth compared with placebo and resulted in earlier hair regrowth and decreased dystrophic hair compared with minoxidil [99].

In addition to the clinical evidence arguing for the benefits of PRP in the management of alopecia, several groups have elucidated parts of the underlying molecular mechanism for how PRP promotes hair growth and regeneration [100–103]. The growth factors in PRP signal through an intracellular cascade involving the PI3K, MAPK/ERK, AKT, and Bcl-2 pathways to regulate cell survival and angiogenesis [100,101]. Li and colleagues [100] are responsible for much of these findings, and their mouse model revealed that activated PRP increases proliferation of dermal papillae cells and stimulates the ERK and AKT pathways, as evidenced by increased expression of FGF-7 and β -catenin, both potent stimuli for hair growth. Furthermore, PRP increases Bcl-2 expression and decreases BAD and BAX expression, suggesting that the net effect of PRP on hair cycling is the prolongation of the anagen phase through inhibition of apoptosis [100,101].

Relative to other cosmetic applications of PRP, the evidence supporting the use of PRP to treat alopecia

is fairly robust given the number of blinded, split-scalp studies and the basic science research into the mechanism of action of PRP. However, the quality of evidence remains inadequate. All the reported studies use a different protocol of PRP isolation, drawing different volumes of blood, centrifuging at different rates and times, and variably using anticoagulants and activating agents. Furthermore, some studies do not report on all components of the isolation technique, specifically how much of the leukocyte layer is taken. Although meta-analyses conducted by Gupta and colleagues [104], Giordano and colleagues [105], and Picard and colleagues [106] identified a benefit of PRP in the management of alopecia, Ayatollahi and colleagues [107] and Gkini and colleagues [108] argued that a meta-analysis could not be conducted because of insufficient and inconsistent reporting of techniques. Overall, although the evidence in support of PRP in the management of alopecia is promising, more robust randomized, double-blinded, placebo-controlled studies with consistent PRP isolation techniques are needed.

Does Platelet-rich Plasma Rejuvenate the Skin?

Because people are living and working longer, the demand for facial rejuvenation procedures and products to restore a youthful appearance by correcting the volume loss and wrinkle formation that occur with aging has greatly increased. With advancing age, collagen synthesis decreases and degradation by matrix metalloproteinases (MMPs) increases, which leads to thinning of the epidermis and dermis and wrinkle formation. A prime target of skin rejuvenating lasers and medications are dermal fibroblasts because they interact with keratinocytes, adipocytes, and mast cells, as well as produce important cytokines and ECM components, such as collagen and glycoproteins [109]. Because dermal fibroblasts are stimulated by growth factors, PRP has been hypothesized to be a stimulator for skin rejuvenation [109–112].

A few animal studies have been conducted to study the effect of PRP on aging skin. Cho and colleagues [109] studied the effect of PRP on UV-B–induced skin wrinkles in mice by randomizing 30 mice subjected to UV-B irradiation for 8 weeks to either no treatment, saline injections, or PRP injections. Relative to the placebo group, the PRP group had significantly greater reduction in wrinkles, fibroblast proliferation, collagen production, and dermal thickness. Kawazoe and Kim [113] demonstrated in mice that PRP with greater concentration of leukocytes provided greater tissue

volumization and wrinkle reduction that was augmented by FGF. Interestingly, Bulam and colleagues [114] found in their study of 24 rabbits that PRP inhibits the effectiveness of botulinum toxins according to EMG analysis.

Unfortunately, the clinical evidence in support of a skin rejuvenating effect of PRP is equivocal and limited. Abuaf and colleagues [115] performed a non-randomized split-face study on 20 women in which PRP was injected on one side and saline on the other with a microneedling technique. Increases in collagen according to mean optical densities were 89% for the PRP group and 46% in the saline group, indicating the previously described role of microneedling in collagen formation and that PRP may have a benefit [115–117]. Gawdat and colleagues [118] performed a randomized split-face study in which 20 women were injected with PRP on one side and growth factors on the other. Both groups had significantly improved skin turgor and vitality and increased epidermal and dermal thickness relative to baseline, but there was no difference between the groups [118]. In contrast, Sevilla and colleagues [119] performed a split-face study on 80 patients and found that growth factor concentrate was superior to PRP. Prospective case series have demonstrated increases in patient satisfaction and subjective physician-reported metrics following topical application or injections of PRP into the nasolabial folds, crow's feet, forehead, malar area, periocular area, perioral area, marionette lines, cheek, jaw, and dorsum of hands [120–130]. Reported histologic changes following PRP include increased epidermal and dermal thickness, reduced solar elastosis, increased elastic fiber formation, increased number of fibroblasts, and increased number of blood vessels [123,124,129]. Ulusal [131] presented a large case series with 94 women with facial aging who were treated with combination PRP and hyaluronic acid fillers via the microneedling technique. The patients benefited from subjective improvements in general appearance, skin texture, and skin firmness [131]. Interestingly, Ulusal [131] observed a decrease in effectiveness of botulinum toxin A injections. Kama-kura and colleagues [132] reported the largest case series with 2005 patients who were injected with PRP plus basic FGF. They reported significant patient- and physician-reported benefits, but that it took an average of 65 days to see an effect [132].

PRP has also been evaluated by multiple groups as an adjunct to laser skin resurfacing for skin rejuvenation. Hui and colleagues [133] performed a split-face study in which 13 women who were being treated with an

ultrapulsed fractional CO₂ laser for facial aging had one side of the face injected with PRP and the other with saline. The PRP group benefited from decreased durations of postlaser erythema, edema, and crusting as well as subjective improvements in wrinkles, skin texture, and skin elasticity [133]. However, there were no differences between the PRP and placebo sides in the objective analysis of skin quality [133]. Shin and colleagues [134] presented 22 patients who were being treated with fractional laser therapy that were randomized to either topical application of PRP or no treatment. They found significant improvement in patient-reported subjective outcomes but no difference in blinded physician analyses [134]. Na and colleagues [135] presented 25 patients who were being treated with CO₂ laser resurfacing on their arms and then had either PRP or saline applied topically. They found the PRP group had faster recovery of transepidermal water loss, indicating quicker recovery of skin barrier function [135].

Unfortunately, adverse reactions associated with PRP used for skin rejuvenation have been reported. Kalyam and colleagues [136] reported a severe complication of permanent monocular blindness in an otherwise healthy woman who received PRP injections for glabellar rhytides. Uysal and Ertas [137] reported experience with PRP causing hyperpigmentation and recommended against using PRP for postinflammatory hyperpigmentation. In general, however, the most common side effects are temporary tenderness, swelling, and bruising.

Although there is a current lack of either preclinical or clinical evidence in support of a skin rejuvenating effect of PRP, several studies have demonstrated that PRP stimulates dermal fibroblasts and therefore may have a role in skin rejuvenation. Cho and colleagues [138] found that PRP increases expression of G1 cell-cycle regulators, type I collagen, and MMP-1 and promotes fibroblast proliferation and migration. Their proposed model postulated that the high concentration of growth factors in PRP stimulate G1 cell-cycle regulators to promote fibroblast proliferation and production of MMP-1s, which degrade the old and poorly organized collagen, and new collagen to replace the existing extracellular framework [138]. Kim and colleagues [139] reported similar findings of increased production of collagen and MMPs with PRP treatment of fibroblasts. Liu and colleagues [140], Kushida and colleagues [141], Roubelakis and colleagues [142], and Kakudo and colleagues [143,144] had similar conclusions regarding the potential stimulatory effect of PRP on dermal fibroblasts.

Although the theory behind PRP for skin rejuvenation is sound, the clinical data do not currently support its

effectiveness, and it is important to understand the inadequacy of the evidence [145–148]. No randomized, placebo-controlled studies have been performed. Furthermore, it is difficult to evaluate the prospective case series given the subjective outcome metrics and the fact that microneedling itself stimulates collagen production. As with PRP use in other cosmetic applications, standardization and consistent use of a PRP isolation protocol is essential, particularly because PRP has been both applied topically and injected for skin rejuvenation. What is particularly important to consider with skin rejuvenation is the timing of PRP treatments. Studies have reported administering PRP as frequently as every week and as infrequently as once every 6 months. Sclafani [120] noted a maximum improvement in wrinkles according to the Wrinkle Assessment Score of 2.12 immediately after treatment, but that improvement decreased to 0.65 at just 1 week. In contrast, Kamakura and colleagues [132] reported not noticing an effect of PRP until more than 2 months after injections. These conflicting findings highlight the benefit of further elucidating the mechanism of PRP's effect on dermal fibroblast and the skin in general. The lifespan of platelets averages around 10 days, and the half-lives of most of its growth factors are on the magnitude of hours, not days [7–9]. Clearly, more research is warranted before PRP can be considered to rejuvenate the skin.

What is the Role of Platelet-rich Plasma as an Adjunct in Cosmetic Surgeries?

Because of PRP's potential hemostatic and wound-healing effects, surgeons have tried using PRP as an adjunct to cosmetic surgeries, primarily facelifts, given the high vascularity of the skin and tissue flaps and risk of hematomas. There are many benefits of a cheap, autologous substance for hemostasis, including prevention of hematoma, reduced surgical time, reduced need for drains, and shorter patient recovery [149,150]. Unfortunately, the evidence in support of a benefit of PRP as a surgical adjunct is limited.

Powell and colleagues [151] conducted a randomized split-face trial on 8 women undergoing rhytidectomy in which half the face was injected with activated PRP before wound closure. They reported a trend toward reduced physician-observed edema and ecchymosis on the PRP side, but the difference was not significant [151]. Man and colleagues [149] prospectively studied 20 patients who received a combination of PRP and fibrin glue before closure following breast augmentation, mastopexy, or rhytidectomy. Their reasoning behind adding fibrin glue was that the fibrinogen concentration in plasma was not high enough to promote hemostasis, and multiple other studies have reported using commercially made fibrin

glues during surgery [149,150]. This group found that capillary bed bleeding sealed within 3 minutes following application of PRP and fibrin glue [149]. Costa and colleagues [152] reported Dr Rohrich's experience with PRP and facelifts. He presently routinely applies PRP following his facelifts in an attempt to reduce postoperative edema and ecchymosis [152]. In his series of 1089 facelifts, 6/502 who did not receive PRP developed a hematoma, compared with 4/586, although this difference was not significant [152]. Giordano and colleagues [150] conducted a meta-analysis of the effect of any tissue sealant—primarily fibrin glue products but also PRP, thrombin and gelatin matrix compounds, polyethylene glycol hydrogels, bovine serum albumin, and so forth, on postoperative hematoma formation. Overall, they reported a relative risk of developing a hematoma of 0.37 when using a tissue sealant [150]. Although there is no evidence that PRP by itself significantly promotes hemostasis, perhaps PRP in combination with additional hemostatic agents, like fibrin, could have a future role as a surgical adjunct. As with other applications, additional rigorous studies are warranted to make definitive conclusions regarding the role of PRP as an adjunct to cosmetic surgical (and other) procedures.

Platelet-rich Plasma in Other Specialties

PRP has been studied extensively in orthopedic surgery and has been used in an attempt to improve healing from bony fractures, tendon injuries, and osteoarthritis, as well as to aid with joint replacement surgery. However, a review of the current literature fails to identify a true benefit of PRP [153–155]. Similarly, many rheumatologists have used PRP for inflammatory joint conditions and have failed to identify a significant effect [156,157]. Oral surgeons and dentists have used PRP to assist with bone grafting, dental implants, osteonecrosis of the jaw, healing after radiation, and as a general adjunct to surgical and dental procedures [158–161]. Other specialties, such as ophthalmology, cardiology, physical medicine and rehabilitation, obstetrics and gynecology, and others, have also experimented with PRP without convincing success [162–165].

ADVERSE EFFECTS OF PLATELET-RICH PLASMA

Because PRP is a concentrated solution of autologous platelets with or without naturally occurring anticoagulants or activating agents, it has generally been thought to be very safe. Most frequently, the side effects are limited to local pain, irritation, erythema, and swelling around the injection site. A case series reported noticing

increased hyperpigmentation following PRP injections to the face and recommended against its use for postinflammatory hyperpigmentation [137]. One significant adverse effect occurred in an otherwise healthy 49-year-old woman who became permanently blind in one eye following PRP injections to the glabellar lines, presumably secondary to central retinal artery occlusion [136].

FUTURE DIRECTION OF PLATELET-RICH PLASMA: TURNING FANTASY INTO FACT

Cosmetic medicine and surgery have evolved tremendously over the past couple of decades and will continue to do so in the future. Currently, the aesthetic field has been captivated by the regenerative and rejuvenating potential of cell-based therapies. Although stem cells and their potential application to cosmetic surgery represent an entire other field of great interest, PRP has emerged as an intriguing new player in aesthetic rejuvenation.

The rationale for the benefit of PRP therapy is clear. The growth factors contained in PRP are known to stimulate and regulate the cells responsible for wound healing and regeneration that decline with age, thus making them attractive targets for rejuvenation. There is also reasonable evidence on the basic science level that PRP effectively promotes wound healing, stimulates fibroblasts and other cells that can rejuvenate the skin, supports ADSCs, and increases angiogenesis to promote fat graft survival, as well as stimulate the pathways responsible for hair growth. Unfortunately, however, the clinical efficacy of PRP in cosmetic medicine and surgery presently remains to be determined.

Most reviews of PRP in cosmetic surgery state that definitive conclusions about the use of PRP cannot be made because of the poor-quality evidence stemming from the lack of large, randomized, placebo-controlled studies. Unfortunately, many of the reported prospective trials and case series are biased because of poor controls, subjective outcome metrics, and significant placebo effects. Furthermore, although most of the published studies report a positive effect of PRP, it is possible that there is a publication bias, and thus, other studies with negative results were not published.

Even among the studies that are randomized controlled trials or internally controlled trials, a major limitation is the significant variability in PRP isolation protocols and their reporting. This limitation has been discussed extensively, yet there has been no effort to standardize protocols. As previously discussed, there are many steps in obtaining PRP, and each of those steps can be performed variably. Multiple groups have reported significant differences in concentrations of

platelets, leukocytes, and growth factors when using different protocols. One would not be surprised if different concentrations and purities of a medication provided variable clinical effects. The same logic applies to PRP, and it would benefit the field if a standardized PRP isolation protocol could be determined and implemented. What is difficult is that no one truly knows, despite a few reports, the optimal platelet, leukocyte, and growth factor concentrations. In addition to standardizing the PRP composition, additional work needs to be performed regarding the timing of PRP administration. Platelets only survive in circulation for about 10 days, and the half-lives of growth factors are typically only a few hours and not more than 24 to 48 hours. Although some say that different preparations of PRP, such as the gel form, facilitate a gradual, sustained release of growth factors, the platelets themselves only last for 10 days and, upon activation, release more than 90% of their stored growth factors. Does this mean that maybe PRP is not being dosed frequently enough, which is why a clinical effect cannot be consistently seen? There is reasonable evidence provided by in vitro studies that PRP and its growth factors can trigger the molecular and cellular processes necessary to achieve the desired cellular stimulation. Unfortunately, the field of PRP therapy has not been able to consistently translate these molecular data to the clinical setting, thereby preventing PRP from establishing itself as a viable rejuvenation product. Until then, the use of PRP therapy in cosmetic surgery will remain a fantasy rather than a fact.

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Updates in Medical Skin Care



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KEYWORDS

• Cosmeceuticals • Topical antiaging • Active cosmetics • Serums • Botanicals • Peptides

KEY POINTS

- Cosmeceuticals attempt to provide some functional skin benefits beyond pure moisturization.
- The vehicle for a cosmeceutical is a moisturizer that makes the skin smooth and soft, increases skin hydration, and improves the optical characteristics of the skin while delivering cosmeceutical ingredients to the skin.
- Ingredients delivered by cosmeceuticals may be vitamins, botanical antioxidants, peptides, skin-lightening agents, and botanical anti-inflammatories.
- These ingredients may enhance cosmetic surgical outcomes, aid in healing, or provide maintenance skin care postprocedure.

INTRODUCTION

Skin care can be medically relevant by providing skin benefits before and after cosmetic surgery. Moisturizers were developed to put lipids back on the skin surface after cleansing, but have now evolved into vehicles to deliver cosmetically active ingredients, creating a category known as cosmeceuticals [1]. Cosmeceuticals are not a recognized product category by the US Food and Drug Administration (FDA) and thus cosmeceuticals are cosmetics, yet can aid in healing and skin comfort post procedure [2]. In 1938 when the FDA created statutory law to define drugs and cosmetics, there was a clear-cut distinction between the 2 categories. Drugs were agents intended to treat and prevent disease, whereas cosmetics dealt with issues of appearance, decoration, and ornamentation. This distinction was adequate until the science of skin physiology advanced. The concept of cosmeceuticals was introduced by Albert Kligman, MD, PhD, in 1984 at the National Scientific Meeting of the Society of Cosmetic Chemists [3]. The

term has now been popularized in both the scientific and consumer communities as a category of skin care products with functional activity. This article examines medical skin care from the cosmeceutical perspective.

TOPICAL COSMECEUTICAL GOALS

Key Points

The goals of a topical cosmeceutical are the following:

- To make the skin feel smooth and soft
- To increase skin hydration
- To improve the optical appearance of the skin
- To deliver cosmeceutical ingredients to the skin

Cosmeceuticals must fulfill 4 basic skin needs in order to be of medical importance: make the skin smooth and soft, increase skin hydration, improve appearance, and deliver a cosmeceutical ingredient to the skin surface [4]. Creating smooth and soft skin uses emollients, which are thin oily substances capable of depositing between the desquamating corneocytes temporarily until the next

Author Disclosure: The author involved with this journal-based CME activity has reported no relevant financial relationship with commercial interests.

Funding Source: None.

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cleansing, at which time they must be reapplied. Many emollients are also moisturizers reducing transepidermal water loss, which may be elevated in the postprocedural setting [5]. Transepidermal water loss is accomplished by placing a water-impermeable film over the skin to retard evaporation and by applying substances to the skin surface to attract water [6]. This increased water content not only creates an optimal environment for healing but also improves facial fine lines of dehydration. In addition, some cosmeceuticals use cosmetic principles by incorporating pigments, such as iron oxide, and optically reflective materials, such as mica or fish scale, to create temporary antiaging appearance benefits.

Topical cosmeceuticals can also deliver ingredients to the skin that can provide benefits complementary to cosmetic surgery. These benefits include skin lightening, peptide delivery, vitamins, and botanicals.

SKIN-LIGHTENING COSMECEUTICALS

Key Points

- Liquiritin in vitro induces skin lightening by dispersing melanin.
- Arbutin is a naturally occurring gluconopyranoside purported to cause decreased tyrosinase activity and inhibits melanosome maturation in vitro.
- Aleosin inhibits tyrosinase by competitive inhibition at the DOPA oxidation site in vitro.
- Vitamin C in vitro interrupts the production of melanin by interacting with copper ions.

Skin lightening may be an important medical skin care benefit because postinflammatory hyperpigmentation is common after the procedure. The most commonly used skin-lightening agent in the current cosmeceutical market is licorice extract, such as liquiritin and isoliquertin, which are glycosides containing flavonoids [7]. Liquiritin in vitro induces skin lightening by dispersing melanin. The second most common cosmeceutical skin-lightening agent is kojic acid, chemically known as 5-hydroxymethyl-4H-pyran-4-one. It is a hydrophilic fungal derivative obtained from *Aspergillus* and *Penicillium* species [8]. The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper [9].

Two other pigment-lightening cosmeceutical ingredients are aleosin and arbutin. Aleosin is a low-molecular-weight glycoprotein obtained from the aloe vera plant. It is a natural hydroxymethylchromone functioning to inhibit tyrosinase by competitive inhibition at the DOPA oxidation site [10,11]. It is sometimes mixed with arbutin, obtained from the leaves of the *Vaccinium vitis-idaea* plant, which is a naturally occurring

gluconopyranoside that causes decreased tyrosinase activity without affecting messenger RNA expression and inhibits melanosome maturation in vitro [12].

Finally, vitamin C is used in some cosmeceutical formulations as a pigment lightening active for its ability to interrupt melanin production by interacting with copper ions to reduce dopaquinone and blocking dihydroquinindol-2-carboxyl acid oxidation [13]. The concentration of vitamin C must be relatively low, however, because it can easily lower pH and cause cutaneous irritation [14].

PEPTIDE-CONTAINING COSMECEUTICALS

Key Points

- Carrier peptides attach to ingredients facilitating transportation of the agent to the active skin site.
- Signal peptides are designed in vitro to increase collagen, elastin, fibronectin, proteoglycan, and glycosaminoglycan production.
- Neurotransmitter peptides are purported to function by inhibiting the release of acetylcholine at the neuromuscular junction.

Peptides are a recently introduced cosmeceutical ingredient, composed of amino acids, which can function as cellular messengers, allowing receptor modulation, activating enzyme release, and regulating the production of proteins. Current peptides belong to the following functional families: carrier peptides, signal peptides, and neurotransmitter peptides [15].

Carrier peptides

The first commercialized peptides were carrier peptides designed to hook to another ingredient and facilitate transportation of the agent to the active site [16]. The first carrier peptide GHK-Cu was designed to deliver copper, a trace element necessary for wound healing [17]. GHK, composed of glycine, histidyl, and lysine, was originally isolated from human plasma and was synthetically engineered. GHK-Cu was commercialized into a line of skin care products, after its original postsurgical use, to minimize the appearance of fine lines and wrinkles based on the in vitro observation of dermal keratinocytes proliferation induction.

Signal peptides

Signal peptides are the most commonly used peptide family in cosmeceuticals. Signal peptides are designed in vitro to increase collagen, elastin, fibronectin, proteoglycan, and glycosaminoglycan production [18]. The most popular signal peptide is palmitoyl pentapeptide,

abbreviated Pal-KTTKS, and is composed of the amino acids lysine, threonine, lysine, and serine. It is a procollagen I fragment demonstrated to stimulate the production of collagen I, III, and IV in vitro [19]. It is used in a low concentration of 4 parts per million, because it theoretically acts as a “signal” whereby one molecule has a cascading effect. The idea is to present the body with procollagen fragments that will downregulate the production of collagenase, thereby increasing dermal collagen, which has been theorized to be of benefit postprocedurally.

Neurotransmitter peptides

Neurotransmitter peptides are purported to function by inhibiting the release of acetylcholine at the neuromuscular junction. They are similar to botulinum toxin in that both selectively modulate synaptosome-associated protein of 25,000 Da, more commonly known as SNAP-25. Botulinum toxin A proteolytically degrades SNAP-25, whereas acetyl hexapeptide-3, a neurotransmitter peptide, mimics the N-terminal end of the SNAP-25 protein that inhibits the SNARE (soluble *N*-ethyl-maleimide-sensitive factor attachment protein receptor) complex formation [20]. Acetyl hexapeptide-3, the most widely commercialized neurotransmitter peptide, in vitro inhibits vesicle docking through prevention of the SNARE complex formation inducing muscle relaxation.

VITAMIN COSMECEUTICALS

Key Points

- Topical over-the-counter (OTC) retinoids include retinol, retinyl esters, and retinyl palmitate, which are commonly used in cosmeceuticals.
- Topical vitamin C can decrease the Minimal erythema dose.
- Topical vitamin E is a frequently used emollient to soothe irritated skin.
- Panthenol, topical vitamin B5, is a humectant drawing water to the skin.

Vitamins are commonly used active ingredients in cosmeceutical moisturizers, which may have value in the cosmetic surgical setting [21]. They are safe for topical application because they can be consumed and are considered foods. The most common topical vitamins are discussed.

Retinoids

Topical cosmeceutical retinoids are synthetic vitamin A derivatives, which include retinol (vitamin A alcohol), retinyl esters, retinoic acid (tretinoin), and retinyl palmitate. Retinoids are biologic modifiers producing

receptor-specific effects, including regulating growth of epidermal cells and promoting differentiation of cell lines [22,23]. They are difficult to topically formulate because of their inherent photo-instability and degradation upon exposure to oxygen.

Retinyl palmitate is the most stable of the vitamin A esters and can be easily incorporated into the oil phase of creams and lotions, because of its lipophilic nature; however, it is not very biologically active [24]. Topical activity of retinyl palmitate is thought to occur following cutaneous enzymatic cleavage of the ester bond and subsequent conversion of retinol to retinoic acid. It is this cutaneous conversion of retinol to retinoic acid that is responsible for the biologic activity of some of the new stabilized OTC retinol preparations. Unfortunately, only small amounts of retinol can be converted by the skin, accounting for the increased efficacy seen with prescription preparations containing retinoic acid [25].

Vitamin C

The active form of vitamin C is *L*-ascorbic acid, which is also light and oxygen sensitive, functioning as an antioxidant by scavenging and quenching free radicals and by regenerating vitamin E from its radical form [26,27]. Some investigators have demonstrated enhanced cutaneous vitamin C levels following topical application of 10% *L*-ascorbic acid; however, this work was performed on a porcine model [28]. Other human studies have demonstrated a decrease in the minimal erythema dose and less erythema following UV-B exposure in subjects treated with topical 10% *L*-ascorbic acid [29]. Vitamin C has also been purported to produce lightening of skin dyspigmentation in the form of magnesium *L*-ascorbyl-2-phosphate [30].

Vitamin E

Vitamin E is a lipid-soluble antioxidant, with alpha-tocopherol possessing greater biologic activity than gamma-tocopherol. Vitamin E is naturally found in the membranes of cells and organelles, preventing oxidation of the polyunsaturated fatty acids of the phospholipids in the membranes by capturing singlet oxygen species [31]. A variety of claims have been made regarding the topical cosmeceutical effects of vitamin E on the skin, to include improved moisturization, increased softness, and better smoothness. Topically applied alpha-tocopherol has been shown to inhibit UV-B-induced edema and erythema, conferring a sun protection factor of 3, after multiple applications [24]. The sun protection factor is thought to be due to its ability to marginally absorb light and function as a

free-radical quenching, lipid-soluble antioxidant [32]. Vitamin E is lipophilic and can be incorporated into cosmeceuticals in the form of vitamin E acetate, the stable esterified form of vitamin E, and vitamin E linoleate.

Niacin

Niacin is one component of the B-vitamin complex, known as vitamin B3. It is an important part of 2 coenzymes of intermediate metabolism nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate. It is found in moisturizers as niacinamide with a variety of purported cosmeceutical effects: sebum inhibition, increased epidermal lipids, reduced inflammation, increased collagen production, increased dermal elasticity, and UV protection [33–35].

Panthenol

Panthenol is the biologically active alcohol form of pantothenic acid, also known as vitamin B5, and is enzymatically converted to pantothenic acid in the skin. It is widely used topically as a cosmeceutical skin conditioning agent. Its function is best characterized as a humectant, because it can both hold and attract water [36].

Four forms of cosmeceutical panthenols are available: D-panthenol, the dextrorotatory isomer; and DL-panthenol, the racemic form; D-calcium pantothenate; and ethyl panthenol. The physiologic activity of the racemic form is 50% less than the dextrorotatory isomer [24]. D-Panthenol is a colorless liquid and DL-panthenol is white crystalline powder, but both are oil insoluble. Panthenol can be used to control viscosity, maintain water content in formulation, increase spreadability, act as a plasticizer, impart better glide, and improve the clarity of gel formulations. In skin preparations, it is usually found at a concentration of 5%.

COSMECEUTICAL BOTANICALS

Key Points

- Botanicals as generally recognized as safe (GRAS) ingredients are easily incorporated into cosmeceutical moisturizers.
- Botanical extracts generally function as antioxidants with associated anti-inflammatory properties.
- Soy, curcumin, silymarin, pycnogenol, and ginkgo possess potent antioxidants that may be used once postprocedural healing has occurred.

Botanicals are frequent cosmeceutical moisturizer additives, delivering the skin benefits summarized in Box 1 [37]. They are GRAS ingredients not requiring FDA approval because they are not consumed as foods. Thus, plant derivatives comprise the most commonly

BOX 1

Purported Botanical Cosmeceutical Benefits

1. Photoprotection against UV-B
2. Quenching of reactive oxygen species
3. Metal chelation
4. Inhibition of targeted enzymes
5. Hormonal modulation
6. Anti-inflammatory activity
7. Microorganism growth inhibition
8. Antioxidant effect of multiple organ systems

used active ingredient category due to their diversity, formulation ease, and presumed safety. Because plants live in a UV-rich outdoor environment, they must all contain antioxidants for survival that can be adapted to provide increased oxidative protection when applied topically on humans [38]. Most antioxidants can also function as anti-inflammatories, which may be relevant

TABLE 1
Botanical Anti-inflammatories

Botanical Ingredient	Formulation Comments
Prickly pear	Mucilage rich in mucopolysaccharides forms protective film
Aloe vera	Mucilage containing 99.5% water and a mixture of mucopolysaccharides and choline salicylate
Bisabolol	Chamomile anti-inflammatory prepared by distillation
Allantoin	Comfrey root or synthetic manufacture from uric acid
Panthenol	Barrier enhancing humectant, vitamin B5
Tea tree oil	Polyphenol anti-inflammatory, cause of allergic contact dermatitis
Evening primrose oil	Polyphenol, high in essential fatty acids
Ginkgo biloba	Polyphenol anti-inflammatory containing ginkgolides, bilobalides
Green tea	Polyphenol anti-inflammatory containing epigallocatechin, epigallocatechin-3-gallate
St. John's wort	Polyphenol anti-inflammatory containing phenolic acid, flavonoids

TABLE 2
Novel Botanical Antioxidants

Common Botanical Name	Chemical Class
Rutin (apples, blueberries)	Flavone
Quercetin (apples, blueberries)	Flavone
Hesperedin (lemons, oranges)	Flavone
Diosmin (lemons, oranges)	Flavone
Mangiferin (mango plant)	Xanthone
Mangostin (bilberry plant)	Xanthone
Astaxanthin (tomatoes)	Carotenoid
Lutein (tomatoes)	Carotenoid
Lycopene (tomatoes)	Carotenoid
Rosmarinic acid (rosemary)	Polyphenol
Hypericin (St. John's wort)	Polyphenol
Ellagic acid (pomegranate fruit)	Polyphenol
Chlorogenic acid (blueberry leaf)	Polyphenol
Oleuropein (olive leaf)	Polyphenol

in postprocedural skin care (Table 1). Botanicals are used to support cosmetic appearance claims purporting the related benefits listed in Box 1.

The list of possible botanicals for inclusion in cosmeceuticals is endless, limited by only the imagination of the cosmetic chemist. Table 2 lists some of the more popular extracts in current use and the chemical class that accounts for their activity [39]. This section discusses some of the more interesting botanicals with current postprocedural relevance, to include soy, curcumin, silymarin, pycnogenol, and ginkgo.

Soy

Fermented soy, found in tofu and roasted soy nuts, contains 2 primary isoflavones: genistein and daidzein. These isoflavones function as phytoestrogens, which are plant-derived estrogens with structural homology to human estrogens. It is theorized that plants generate estrogens to reduce male mammal fertility, preventing extinction from overgrazing. Orally consumed soy has been associated with the decrease in cardiovascular disease and breast cancer seen in Asian women [40,41]. Topical genistein may function as an antioxidant scavenging peroxy radicals and protecting against lipid peroxidation in vivo [42]. A study in mice documented the ability of soy to protect against UV-B–induced skin damage where a topical application of non-denatured soy extracts reduced UV-B–induced cyclooxygenase-2

expression, reduced prostaglandin-E2 secretion, and inhibited p38 MAP kinase activation [43]. It is unknown whether these rodent data translate into UV-B photoprotection in humans.

Curcumin

Curcumin is a botanical used as a spice and rediscovered as a topical antioxidant. It is used in cosmetics as a natural yellow coloring derived from the rhizome of the tumeric plant. Tetrahydrocurcumin, a hydrogenated form of curcumin, is off-white in color and can be added to skin care products as a natural preservative to prevent moisturizer lipid rancidity. The antioxidant effect of tetrahydrocurcumin is said to be greater than vitamin E. The skin benefits accrue when curcumin quenches oxygen radicals and inhibits nuclear factor-KB [44].

Silymarin

Another family of flavonoids comes from the milk thistle plant (*Silybum marianum*), which belongs to the aster family of plants that includes daisies, thistles, and artichokes. The cosmeceutical extract is termed silymarin and contains 3 flavonoids derived from the fruit, seeds, and leaves of the plant. These flavonoids are silybin, silydianin, and silychristine, which possess antioxidant effects demonstrated topically in hairless mice by the 92% reduction of skin tumors following UV-B exposure [45]. The mechanism for this decrease in tumor production is unknown, but topical silymarin has been shown to decrease the formation of pyrimidine dimers in a mouse model and improve healing of burn wound in albino rats [46,47]. A double-blind placebo-controlled study in 46 subjects with rosacea found improvement in skin redness, papules, itching, hydration, and skin color, which was postulated to be due to direct activity on cytokine and angiokine activity [48].

Pycnogenol

Pycnogenol is an extract of French marine pine bark (*Pinus pinaster*), which grows only on the southwest coast of France in Les Landes de Gascogne. The extract is a water-soluble liquid containing several phenolic constituents, including taxifolin, catechin, and procyanidins. It also contains several phenolic acids, including p-hydroxybenzoic, protocatechuic, gallic, vanillic, p-courice, caffeic, and ferulic [49]. It is a potent free-radical scavenger that can reduce vitamin C radicals, returning the vitamin C to its active form [50]. The active vitamin C in turn regenerates vitamin E to its active form maintaining the natural oxygen scavenging mechanisms of the skin [51].

Ginkgo

Ginkgo biloba, also named the maidenhair tree, is the last member of the Ginkgoaceae family, which developed some 200 to 250 million years ago. For this reason, ginkgo contains flavonoids not found in other botanicals. It possesses bilobalide (a sesquiterpene), ginkgolides (diterpenes with 20 carbon atoms), and other aromatic substances such as ginkgol, bilobdol, and ginkgolic acid. The plant leaves are said to contain unique polyphenols such as terpenoids (ginkgolides, bilobalides), flavonoids, and flavonol glycosides that have anti-inflammatory effects. These anti-inflammatory effects have been linked to antiradical and antilipoperoxidant effects in experimental fibroblast models [52]. Ginkgo flavonoid fractions containing quercetin, kaempferol, sciadopitysin, ginkgetin, and isoginkgetin have been demonstrated to induce human skin fibroblast proliferation in vitro. Increased collagen and extracellular fibronectin were also demonstrated by radioisotope assay [53].

SUMMARY

Cosmeceuticals may offer important benefits in the cosmetic surgery setting. Wound healing may be enhanced by the use of moisturizers designed to create an optimal environment for wound healing. Moisturizers can also place a protective barrier over wounded skin to assist in pain management. Moisturizers combined with active ingredients, such as botanicals, can function as anti-inflammatories minimizing postprocedure erythema. Although this is currently speculative until more data are obtained, technologies, such as copper peptides adapted from prescription wound-healing devices, may also be helpful postprocedurally. However, cosmeceuticals perhaps are most useful in the postprocedure arena to allow the patient to remain proactive in their skin care to maintain an optimal appearance.

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Patient Safety Issues



Venous Thromboembolism Prophylaxis by the Data

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KEYWORDS

- Aesthetic surgery • Cosmetic surgery • Aesthetic plastic surgery • Surgical complications
- Postoperative complications • Venous thromboembolism • Deep vein thrombosis

KEY POINTS

- Venous thromboembolism is the leading cause of death in outpatient surgical patients. Most deep vein thromboses present asymptomatic; therefore, a high level of suspicion by the surgeon is necessary.
- Individualized risk stratification with the appropriate risk assessment tool is critical to help guide decision-making on chemoprophylaxis.
- Consideration should be given to other procedure risk factors not included in the Caprini score, including body region, combined procedures, and type of anesthesia.
- In addition to mechanical prophylaxis and chemoprophylaxis, preoperative optimization should be considered in all cosmetic patients, including weight loss, discontinuation of endogenous estrogen, and possible need for hematology assessment in high-risk patients.
- A fixed dose for chemoprophylaxis might not be adequate coverage for patients, and monitoring of the heparin activity may allow optimization of the dose.

INTRODUCTION

Venous thromboembolism (VTE), defined as deep vein thrombosis or pulmonary embolism, is a complication that has gained much interest and attention in the plastic surgery field in recent years. Because of the high morbidity and mortality that accompanies VTE, a great deal of emphasis is being placed on patient stratification and disease prevention [1–3]. It is for this reason that in 2009 the Venous Thromboembolism Prevention study was funded by the Plastic Surgery Foundation,

and in 2011 the American Society of Plastic Surgeons approved the Venous Thromboembolism Task Force [4]. Equally, in 2016, the American Association of Plastic Surgeons released a meta-analysis of VTE stratification as well as the risks and benefits of stratification [5].

According to the Centers for Disease Control and Prevention (CDC), it is estimated that as many as 900,000 Americans have a VTE yearly with an estimation of 60,000 to 100,000 deaths. For patients presenting with symptomatic pulmonary embolus, 10% will

Disclosure Statement: Dr J.C. Grotting is a founder and shareholder of CosmetAssure (Birmingham, AL), an author for Quality Medical Publishing (St Louis, MO) and Elsevier (New York, NY), and a shareholder of Keller Medical (Stuart, FL) and Ideal Implant (Dallas, TX). The other authors have nothing to disclose.

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be dead within 60 minutes [1,3,6–8]. However, because of the silent nature of the disease along with the low rate of conducted autopsies in the United States, VTE incidence statistics are likely greatly underestimated. It is estimated that only 33% of patients with deep vein thrombosis present with symptoms [7,9]. Current estimates put the prevalence of VTE (symptomatic or silent) at up to 15% to 40% in general surgery, 15% to 40% in gynecologic surgery, 15% to 40% in neurosurgery, 40% to 60% in orthopedic surgery, and 40% to 80% in major trauma cases [2,10].

In the postsurgical setting, VTE can have significant sequelae, leading to extended hospital stays that can burden both patients and hospital systems [6,7]. It can also have long-term consequences to patients from damage to the venous vessel walls and venous valves leading to increased risk of recurrence, chronic venous reflux, and postthrombotic syndrome. It is not surprising that all these can negatively impact the quality of life of the affected patients. Severe postthrombotic syndrome can occur in approximately 10% of patients following deep vein thrombosis and manifest as a chronically swollen, tender, and ulcerated extremity. This syndrome is considered a major predictor of poor quality of life after deep vein thrombosis [11]. It is equally estimated that one-third of patients with a VTE will have a recurrence within 10 years [6].

Studies have shown that outpatient and ambulatory surgical cases are very safe, with an incidence of VTE for all specialties ranging from 0.001% to 0.15% [12,13]. Although most elective cosmetic plastic surgery cases fall into this group, the American Society of Plastic Surgeons estimates at least 18,000 annual cases of deep vein thrombosis in all plastic surgery procedures across the country, based on extrapolation from other surgical groups [2,9]. However, this does not separate cosmetic surgery patients from reconstructive plastic surgery patients, who more often have complications [14]. In general, there is significant variation in patient populations and practitioner's subspecialties within plastic surgery, which accounts for a great variation in prevalence rates. This point was also stated in a recent review that reported an 18-fold variation in VTE over the entire plastic and reconstructive surgery population [3]. Surgeon surveys, largely voluntary, have reported VTE incidences following cosmetic surgery ranging from 0.012% to 2.0% [10,11]. In addition, a large study from the CosmetAssure database found an overall major VTE rate of 0.09% following cosmetic procedures, with significant procedure-specific rate differences as well as procedure combination differences [15].

With the increased attention on VTE, there has been an increased push to elucidate risk factors in cosmetic

surgery cases in order to corroborate recommendations for surgical risk assessment and prophylaxis. The Caprini Risk Assessment Model was specifically developed for assessing perioperative and 60-day postoperative thrombotic risk after surgery. The American Society of Plastic Surgeons has approved the Caprini Risk Assessment Model and other risk assessment tools to better identify high-risk plastic surgery patients, mostly in those undergoing reconstructive procedures [4,16–19]. However, despite this, many plastic surgeons may fail to recognize risk factors for VTE when present and do not follow the American Society of Plastic Surgeons' guidelines for preoperative VTE prevention and treatment, which results in underuse of chemoprophylaxis in high-risk patients.

INDIVIDUALIZED RISK STRATIFICATION

Individualized risk stratification is a concept that has been widely accepted because of the wide variability of the plastic surgery patient population. Patient factors (eg, age, past and current medical history, medications, immobilization) and surgical factors (eg, minor surgery vs major surgery) are used to identify high-risk patients and help guide decision-making on the possible need for mechanical prophylaxis and chemoprophylaxis. This finding is supported by the ninth edition of the "American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" published in 2012 [3,16,20].

Multiple individualized risk assessment models have been developed and evaluated; however, none have been more validated than the Caprini Risk Assessment Model that was first published in 1991 and subsequently updated to reflect improved understanding of VTE [21,22]. Such a model is weighted based on different patient and operative risk factors because certain risk factors are known to contribute more than others. The 2005 version has been validated for the assessment of perioperative as well as 30-day and 60-day postoperative thrombotic risk in plastic and reconstructive surgery (Fig. 1). It has also been validated in multiple other surgical disciplines, including general surgery, vascular surgery, urology, gynecology oncology, otolaryngology, thoracic surgery, spine surgery, and patients in the surgical intensive care unit [3]. The model was updated again in 2010, but the 2005 Caprini Risk Assessment Model remains the better predictor of VTE risk in adult plastic surgery patients [11,16].

In 2011, Pannucci and colleagues [11] published the results of the Venous Thromboembolism Prevention Study Network demonstrating that patients with higher Caprini scores have a significantly higher likelihood of

Thrombosis Risk Factor Assessment

Patient's Name: _____ Age: ____ Sex: ____ Wgt: ____ lbs

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Choose All That Apply

Each Risk Factor Represents 1 Point

- ☐ Age 41–60 y
- ☐ Minor surgery planned
- ☐ History of prior major surgery (<1 mo)
- ☐ Varicose veins
- ☐ History of inflammatory bowel disease
- ☐ Swollen legs (current)
- ☐ Obesity (BMI >25)
- ☐ Acute myocardial infarction
- ☐ Congestive heart failure (<1 mo)
- ☐ Sepsis (<1 mo)
- ☐ Serious lung disease incl. pneumonia (<1 mo)
- ☐ Abnormal pulmonary function (COPD)
- ☐ Medical patient currently at bed rest
- ☐ Other risk factors _____

Each Risk Factor Represents 2 Points

- ☐ Age 60–74 y
- ☐ Arthroscopic surgery
- ☐ Malignancy (present or previous)
- ☐ Major surgery (>45 min)
- ☐ Laparoscopic surgery (>45 min)
- ☐ Patient confined to bed (>72 h)
- ☐ Immobilizing plaster cast (<1 mo)
- ☐ Central venous access

Each Risk Factor Represents 5 Points

- ☐ Elective major lower extremity arthroplasty
- ☐ Hip, pelvis or leg fracture (<1 mo)
- ☐ Stroke (<1 mo)
- ☐ Multiple trauma (<1 mo)
- ☐ Acute spinal cord injury (paralysis)(<1 mo)

Each Risk Factor Represents 3 Points

- ☐ Age >75 y
 - ☐ History of DVT/PE
 - ☐ **Family history of thrombosis^a**
 - ☐ Positive Factor V Leiden
 - ☐ Positive Prothrombin 20210A
 - ☐ Elevated serum homocysteine
 - ☐ Positive lupus anticoagulant
 - ☐ Elevated anticardiolipin antibodies
 - ☐ Heparin-induced thrombocytopenia (HIT)
 - ☐ Other congenital or acquired thrombophilia
- If yes:
 Type _____

For Women Only (Each Represents 1 Point)

- ☐ Oral contraceptives or hormone replacement therapy
- ☐ Pregnancy or postpartum (<1 mo)
- ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score

FIG. 1 The 2005 Caprini score. BMI, body mass index; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolus. ^a Most frequently missed risk factor. (From Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon* 2005;51(2–3):73; with permission.)

VTE events following plastic surgery. Specifically, it was shown that patients with a Caprini score greater than 8 had a significantly increased risk for VTE when compared with lower scores. Approximately 1 in 9 patients (11.3%) with Caprini scores greater than 8 had a VTE event within

60 days after surgery when chemoprophylaxis was not provided. This study also demonstrated the risk of VTE being well beyond the immediate postoperative period. Likewise, the UK Million Women Study revealed that the VTE risk in middle-aged women may remain elevated

for at least 90 days after surgery and possibly up to a year [23]. Pannucci and colleagues [16] also analyzed the 2010 modifications to the Caprini Risk Assessment Model, which included the addition of new risk factors and the reweighing of old risk factors into the score. They found that the 2010 Caprini Risk Assessment Model failed to risk stratify adult plastic surgery patients as well as the 2005 model. The 2010 model overinflated the plastic and reconstructive patients' perceived risk score by disproportionately weighing the operative time and body mass index [3,16].

Although the Caprini Risk Assessment Model is an effective tool for risk stratification, it is important to note that certain factors that other studies have found to be associated with VTE are not considered in the 2005 and 2010 Caprini Risk Assessment Model; therefore, clinical judgment needs to be equally used. These factors include inpatient procedures compared with outpatient, procedure-specific risks, body regions, and combined procedures [15].

Inpatient/Outpatient Surgery

A major transition that many specialties, including plastic and reconstructive surgery, has seen in the last couple of decades is a shift toward early patient discharge and many procedures being performed on an outpatient basis. This shift is still evolving, especially with the introduction of newer technology and analgesic modalities. A prime example is the recent popularity of long-acting liposomal bupivacaine, which has further enhanced this push. This popularity has been largely driven by an emphasis on cost-effective quality initiatives that have encouraged several institutions around the country to consider these quality measures [24–37]. Since the 1980s, there has been a steady decline in surgeries performed in hospitals, from 90% to 45% [38]. Concurrently, from 1995 to 2005, office-based procedures have doubled to approximately 10 million cases per year [39]. According to the American Society for Aesthetic Plastic Surgery, there was a 5.6% increase (from 56.3% to 61.9%) in cosmetic procedures performed in the office-based setting from 2014 to 2015 alone [40]. This finding was also confirmed by a study from the CosmetAssure database, which examined 129,007 patients between 2008 and 2013 and revealed that 66.4% of all cosmetic procedures were performed in either an accredited surgical center or office-based surgical suite [15].

The previously mentioned UK Million Women Study, which encompassed 947,454 patients, demonstrated that the VTE incidence was significantly higher after inpatient surgery compared with outpatient procedures [23]. The risk was highest in the first 6 weeks

after inpatient surgery, reaching a peak at the third post-operative week (110-fold greater than the baseline). This risk remained elevated for up to 10 to 12 months post-operatively. Outpatient surgery had a lower rate of VTE than inpatient but was still significantly increased at 10-fold greater than the baseline for the first 6 weeks after surgery. Pannucci and colleagues [13] analyzed the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database between 2005 and 2009 for the adult outpatient surgery population (outpatient surgery or 23-hour observation) and identified a 20-fold variation in 30-day VTE risk between low-risk (0.06%) and high-risk (1.18%) patients. It is also important to note that in an analysis of the American Association for Accreditation of Ambulatory Surgery Facilities, 23 deaths were identified following 1,141,618 procedures, 13 (57%) of which were attributed to pulmonary embolus [41]. For these reasons, the American Society of Plastic Surgeons VTE task force recommends that surgeons should consider completing a Caprini risk assessment for the outpatient procedure population, even though the 2005 Caprini Risk Assessment Model has only been formally validated for the inpatient plastic surgery population [4].

Procedure-Related Risk

Body contouring procedures have been shown to be associated with the highest rate of thromboembolic disease in cosmetic procedures [18]. Previously, abdominoplasty alone and combined with another surgical procedure was thought to be the cosmetic procedure most associated with death from pulmonary embolus [41,42]. During these procedures, intra-abdominal pressure increases from internal plication and fascial tightening, which in addition to abdominal binder tightening and decreased ambulation from pain, is thought to predispose patients to venous thrombosis. However, a recent study from the CosmetAssure database found that the highest incidence of a major VTE event following a single procedure was thigh lift (0.25%), followed by lower body lift (0.23%) and then abdominoplasty (0.20%) [15]. It was also noted that body procedures were responsible for 93.1% of all confirmed VTE and had a relative risk of 12.9, the highest of any independent risk factor. Hatf and colleagues [18] acknowledged this increased risk in body lift/circumferential abdominoplasty and abdominoplasty with intraabdominal procedures and proposed the addition of these procedures as a specific risk factor to emphasize the VTE risk and prophylaxis need. Wes and colleagues [43] specifically evaluated the risk of VTE in body contouring procedures through the

ACS-NSQIP database and found an odds ratio of 2.75 specifically in trunk contouring as well as an increased risk in age equal to or greater than 45 years, body mass index equal to or greater than 30 kg/m², and patients requiring inpatient admission. This study also included both plastic surgeons and general surgeons and demonstrated an increased risk of VTE in general surgeons performing body contouring procedures.

Another important concept is that of combined procedures, which has received publicity with the presumed advantage of a single recovery period and reduced surgical cost. The authors have previously demonstrated through the CosmetAssure database that 70.7% of all VTEs occurred in patients who underwent combined procedures, and combined procedures had a relative risk of 2.4, the second highest risk factor after body procedures [15]. Additionally, the authors observed an increased risk of VTE in a stepwise manner with the number of procedures: 1 procedure (0.04%), 2 procedures (0.16%), 3 procedures (0.26%), and 4 procedures (0.53%). Likewise, Wes and colleagues [43] analyzed the ACS-NSQIP database and demonstrated that for body contouring procedures there was an increased risk of VTE for 2 regions contoured (odds ratio 1.64) and for more than 2 regions contoured (odds ratio 4.01). Whether this increased risk of VTE is related to the prolonged operative duration or from the increased surgical injury is yet to be determined.

Finally, the type of anesthesia used during a procedure may have an effect on the VTE risk. Multiple studies have demonstrated general anesthesia, specifically muscle paralysis, may result in venous stasis in the lower legs and predispose to VTE [3,44,45]. The American Association of Plastic Surgeons' consensus statement gives a grade 1C recommendation (strong recommendation, low or very quality evidence) for using "non-general anesthesia when appropriate. When possible, consideration should be given to using monitored anesthesia care, local anesthesia with sedation, or neuraxial anesthesia instead of general anesthesia." [5]

It is important to note that although the 2005 Caprini Risk Assessment Model has been validated in the plastic surgery population, it fails to include certain procedure-specific risk factors, such as body region, combined procedures, or type of anesthesia [3,5,15,18]. Clinical judgment needs to be used to assess patients who might have additional risk factors.

PREOPERATIVE OPTIMIZATION

Preoperative VTE risk optimization should be considered on every cosmetic patient, as these are elective

procedures and patient safety should always be considered a priority. Because of the high morbidity and mortality that accompanies VTE, operations can safely be delayed or staged to help address potential risk factors. It is important to realize that the 2005 Caprini Risk Assessment Model was developed to stratify both medical and surgical patients of all specialties. Many factors included in the 2005 Caprini score should be considered exclusion factors for elective cosmetic surgery. Examples include sepsis (<1 month); serious lung disease, including pneumonia (<1 month); acute myocardial infarction; stroke (<1 month); multiple trauma (<1 month); hip/pelvic or leg fracture (<1 month); pregnancy or post partum (<1 month); and so forth. [21].

Some of the preoperative modifiable Caprini factors include obesity and oral contraceptive or hormone replacement therapy. Obesity has been shown previously to increase venous stasis and decrease venous return through altered lower extremity venous hemodynamics and increased intra-abdominal pressure [13,16,46]. A study using the CosmetAssure database has shown a trend of a statistically significant increase in VTE incidence in the overweight (0.14%), obese (0.24%), and morbidly obese (0.22%) compared with patients with a body mass index of 18.5 to 24.9 kg/m² (0.04%) [15]. Both overweight (body mass index 25.0–29.9 kg/m²) and obesity (body mass index ≥30 kg/m²) were shown to be independent predictors of VTE with relative risks of 1.67 (95% confidence interval [CI] 1.07–2.61) and 2.56 (95% CI 1.60–4.14), respectively. Stein and colleagues [47] investigated 12,015,000 patients, both obese and nonobese, in the National Hospital Discharge Survey during a 21-year period (1979–1999) and found a relative risk of deep vein thrombosis of 2.4 and pulmonary embolus of 2.21 in obese patients. They also reported that obesity had the greatest impact on the risk of VTE in patients aged less than 40 years as well as on females more than males.

Increased estrogen levels have been shown to lower levels of protein S, which contribute to thrombosis [2]. Further, estrogen can activate the endogenous fibrinolytic system, perhaps leading to procoagulant effects and resistance to anticoagulants like protein C [15,48,49]. Women taking an oral contraceptive pill with both estrogen and progestin, which according to the CDC is the case in 17.1% of all women in the United States, have been shown to have a 2- to 3-fold increased risk of VTE [2,15,50]. Although hormone replacement therapy has a lower biological potency than oral contraceptive pills, with estrogen levels 80% to 85% lower, it still entails an increased VTE rate of 2- to 4-fold [51]. This finding is also seen in men taking

estrogen therapy for prostate cancer [15,51]. When this preoperative risk factor is identified in patients, it can be stopped 4 weeks before surgery and restarted 4 weeks after surgery.

High-risk patients, based on personal or strong family history of hypercoagulability, may be best assessed by a preoperative consultation with a hematologist for assistance with perioperative VTE risk modification and chemoprophylaxis [3].

VENOUS THROMBOEMBOLISM PREVENTION STRATEGIES

VTE prevention strategies include mechanical devices and chemoprophylaxis. Mechanical devices can be broken down into passive and active mechanical methods of prophylaxis. Passive methods include graduated compression stockings; it is thought that these reduce the deep vein thrombosis risk by shunting blood to the deep venous system, increasing the velocity of venous flow, and improving valve function [2,5]. In a Cochrane review, this was demonstrated to be superior to no stockings at all in the prevention of deep vein thrombosis and pulmonary embolus [52]. It is important for graduated compression stockings to be properly fitted to patients, and patients should be educated for proper application [2].

Active mechanical devices include sequential compression devices and venous foot pumps. Intermittent pneumatic compression devices are thought to work by preventing venous pooling and stasis, stimulating fibrinolytic activity, and increasing release of tissue plasminogen activator [2]. In 2013, a meta-analysis concluded that the active mechanical method with sequential compression devices is superior to elastic compression stockings at VTE reduction (odds ratio 0.61). It equally concluded that sequential compression devices combined with chemoprophylaxis were more effective than sequential compression devices alone [53]. It is for this reason that a meta-analysis and the consensus conference by the American Association of Plastic Surgeons recommended the use of intermittent pneumatic compression to prevent perioperative VTE events in plastic surgery patients [5].

The most widely used chemoprophylaxis for prevention of VTE is heparin, in the form of either low-molecular-weight heparin or low-dose unfractionated heparin. Enoxaparin, a low-molecular-weight heparin, has become the most common choice of VTE prevention because of its once-daily administration and more predictable dose response. The aforementioned American Association of Plastic Surgeons' guidelines do not

recommend adding routine chemoprophylaxis to intermittent pneumatic compression for VTE prevention in non-risk-stratified plastic surgery patients. They recommended that all plastic surgery patients be individually risk stratified using the 2005 Caprini score and to consider chemoprophylaxis for patients with a Caprini score greater than 8 [5]. The American Society of Plastic Surgeons' recommendations state that chemoprophylaxis should be strongly considered for patients with 2005 Caprini scores of 7 or greater. Based on the aforementioned data, it is thought that chemoprophylaxis should be provided for patients with a 2005 Caprini score of 7 or greater [3,4]. Unfortunately, there are no strong data with regard to the optimal duration of chemoprophylaxis, especially for outpatient surgeries. In certain occasions, such as in patients with a recognized hypercoagulable state not clearly characterized by the 2005 Caprini score, a preoperative hematology consultation may be extremely valuable to assist with hypercoagulability workups as well as perioperative VTE risk modification and chemoprophylaxis. Although the apparent risk of bleeding is a concern for plastic surgeons, several studies have shown rates of reoperative hematomas to be less than 1% after use of chemoprophylaxis, with only a minority of studies demonstrating statistically significant differences [5,54,55].

FUTURE AVENUES

Monitoring for Adequacy of Chemoprophylaxis

Fixed-dose low-molecular-weight heparin prophylaxis has long been the standard in several surgical specialties. The Plastic Surgery Foundation-funded Venous Thromboembolism Prevention Study revealed a 14-fold variation in VTE risk among the overall plastic surgery population, but patients with Caprini scores greater than or equal to 7 receive significant VTE risk reduction when postoperative enoxaparin was provided [11,16,21,54,56,57]. Despite this aggressive prophylaxis approach, a considerable proportion of patients in this study had VTE events. Interestingly, VTE events were also noted in patients at lower risk levels of the Caprini risk assessment despite low-molecular-weight heparin prophylaxis. Unfortunately, existing evidence does not fully explain why chemoprophylaxis is still ineffective for some patients and breakthrough VTE events still occur, despite strict adherence to current guidelines [4,5]. This finding may have important implications in patient care and safety after aesthetic surgery.

Given the long half-life and high bioavailability of low-molecular-weight heparin after administration, the

current manufacturer recommendations do not require monitoring unless patients are pregnant, morbidly obese, or have renal failure [58]. Nevertheless, recent literature suggests that monitoring, although not required, may allow optimization of enoxaparin dose [3,59,60]. The anti-factor Xa level has been proposed as a marker for monitoring enoxaparin activity [61–63]. In fact, it has been shown that the peak anti-factor Xa level, determined at 4 hours after subcutaneous injection, is the most accurate marker of enoxaparin activity and safety [61–63]. A peak range of 0.2 to 0.4 IU/mL for twice-daily dosing has been reported as safe and effective for numerous surgical populations [60,62,64–67]. However, previous studies of various surgical populations have demonstrated the inadequacy of fixed prophylactic doses of enoxaparin to achieve target anti-factor Xa levels [68]. This finding becomes even more relevant because inadequate enoxaparin dosing that results in low anti-factor Xa peak levels has been associated with both symptomatic and asymptomatic VTE events in surgical patients [61,62,64,68,69]. Further studies are needed to better evaluate the effect of adjusting the dose and frequency of enoxaparin on anti-factor Xa levels and, more importantly, the subsequent impact on VTE and bleeding events.

Although the anti-factor Xa level is considered to be the gold standard for low-molecular-weight heparin monitoring, it represents only an indirect measure of the amount of low-molecular-weight heparin in the plasma and does not directly measure the anticoagulant effect [70,71]. It describes pharmacokinetics rather than pharmacodynamics. Previous studies have advocated the use of a thrombin generation assay to monitor the effect of low-molecular-weight heparin because generation of thrombin is a key event in the coagulation process and depends on factor Xa [70]. As a result, thrombin generation assay may reflect the anticoagulation effect of low-molecular-weight heparin more accurately, as it accounts for both the indirect inhibition of factor Xa and the direct inhibition of thrombin itself.

Other chemoprophylactic agents that have gained popularity over the last few years include orally active medications that specifically inhibit either factor Xa or thrombin. These new anticoagulants have undergone extensive evaluation in orthopedic patients with favorable results from a number of phase III studies, but they have not been well studied for VTE prevention in plastic surgery patients [72–74]. From a practical standpoint, these agents have become an attractive option for physicians and patients because they are administered orally and there is no need for monitoring. However, it is still unclear if the currently proposed prophylactic

doses are protective for all patients. Additional research is necessary to establish the optimal dosing as well as the true safety and efficacy of these new agents compared with conventional VTE prophylaxis.

Is the 2005 Caprini Risk Assessment Model Accurate for Cosmetic Surgery?

Although several individualized risk-stratification tools have been proposed for inpatient and outpatient surgical populations, the 2005 Caprini Risk Assessment Model is the most-validated and widely used tool for plastic surgery patients and is the one recommended by both the American Society of Plastic Surgeons and the American Association of Plastic Surgeons [4,5]. In 2010 a modified Caprini Risk Assessment Model was made available, but it was actually found to result in a less accurate risk stratification for plastic surgery patients [16]. Even the 2005 Caprini Risk Assessment Model is not specifically designed for the subset of healthier cosmetic patients and, thus, does not include some of the risk factors and protective factors that are more relevant to this patient population, such as recent prolonged air or car travel, anesthesia type, abdominal wall plication, combining aesthetic surgery procedures, use of compression garments postoperatively, and extent of early postoperative ambulation.

Also, as previously discussed, the 2005 Caprini Risk Assessment Model has not been validated for outpatient procedures. Furthermore, it does not take into account whether patients had inpatient or outpatient surgery, which has been shown to carry a different risk profile for VTE as demonstrated by the Million Women Study from the United Kingdom [23]. Interestingly, the American Society of Plastic Surgeons Venous Thromboembolism Task Force recommended that surgeons “should consider completing” a 2005 Caprini score or a similar risk assessment tool for VTE risk stratification for outpatient surgery patients as opposed to a should-complete approach for inpatient surgery patients [4].

The 2005 Caprini Risk Assessment Model fails to include specific procedures or body regions, which have been previously shown to be important consideration for VTE in cosmetic procedures. Several prior studies, as discussed earlier, have found increased odds of VTE in patients undergoing body procedures, such as abdominoplasty, thigh lift, and lower body lift [15,18,43]. Some investigators have even proposed the incorporation of these procedures to a risk assessment model as risk factors in order to better quantify the VTE risk [18]. Perhaps unmodified garments can create a tourniquet effect on the upper thighs that decreases lower extremity venous outflow and, thus,

predispose to thrombosis. It is also possible that the findings of the aforementioned studies are partially related to increased intra-abdominal pressure, which has been observed following abdominal plication in abdominoplasty, during bed flexion to facilitate fascial and skin closure in abdominoplasty, and with the use of abdominal binders after contouring procedures [75–77]. Increased intra-abdominal pressure is known to create lower extremity venous stasis and venous dilation, which can further lead to intimal microtears providing a nidus for clot formation [78–80]. Further research is necessary to better establish risk factors for VTE in aesthetic surgery patients to create a more comprehensive risk assessment model that will more accurately quantify the risk and further optimize recommendations for prophylaxis for this patient population.

SUMMARY

In 2007, a survey by Broughton and colleagues [81] demonstrated that VTE prophylaxis is used continuously by only 48.7% of surgeons performing facelifts, 43.7% of surgeons performing liposuction, and 60.8% performing combined procedures. Another study around the same time found that 39% of respondents were not aware of current VTE prophylaxis recommendations [82]. These studies support the strong need for surgeon education of individualized patient risk stratification, preoperative optimization, and prevention strategies. Equally, with 10% of patients with symptomatic pulmonary embolus dying within 60 minutes, early diagnosis with immediate and aggressive treatment is imperative [7].

Individualized risk stratification of patients for VTE does not only allow plastic surgeons to identify both low-risk and high-risk patients but it also helps guide the need for VTE prophylaxis and provides patient education. The 2005 Caprini Risk Assessment Module is the most widely used and validated risk stratification tool in plastic surgery patients. However, it is important to note that certain procedure-specific risk factors are not captured in the score, such as body region, combined procedures, and type of anesthesia. Therefore, clinical judgment needs to be used to identify patients who might be of higher risk. Currently, it is recommended that plastic surgery patients are risk stratified individually using the 2005 Caprini score. In addition, active mechanical VTE prophylaxis (intermittent pneumatic compression) should be used for all patients, and chemoprophylaxis should be strongly considered for patients with Caprini scores of 7 or greater.

Even though fixed-dose low-molecular-weight heparin has been the standard approach for chemoprophylaxis in plastic surgery patients, recent literature suggests that monitoring its activity may allow optimization of the dose. The anti-factor Xa level has been proposed for monitoring; but other newer methods are emerging, such as thrombin generation assay. Further research is necessary to better evaluate the effect of adjusting the dose and frequency of the chemoprophylactic agent on these monitoring methods and, more importantly, the subsequent impact on VTE and bleeding events. In addition, the role of orally active medications for chemoprophylaxis, some of which are gaining acceptance in other surgical specialties, deserves further evaluation.

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